Exploring the natural history and determinants of chronic respiratory disease in high-risk populations: perspectives from the UK and Malawi

Thesis submitted in accordance with the requirements of the Liverpool School of Tropical Medicine for the degree of Doctor in Philosophy

By

Rebecca Nightingale

October 2020
Declaration

I hereby declare that this PhD these is a presentation of my original research work. Material contained herein has not been previously published, accepted or presented for the award of any University degree. Wherever contributions of others are involved, every effort has been made to indicate this clearly, with due acknowledgement to the relevant sections made in the thesis.
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A note about COVID-19. It is nearly impossible to hand in a respiratory thesis without a mention of the impact of COVID-19. There was minimal impact on overall data collection. The study in Chapter 6 was cut one month short for safety reasons and this has been stated as part of the patient flow diagram in the paper. The impact of COVID-19 on the populations described in this thesis is not known yet. Personally I have written this thesis whilst also working clinically in Liverpool, which has resulted in some delay in my original timeframe and sadly, due to travel restrictions, I have yet to return to Malawi to provide participant feedback for the study reported in Chapter 6. It is hoped that this will become possible in 2021.
### Table of Abbreviations

Abbreviations listed in alphabetical order

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACO</td>
<td>Asthma-COPD Overlap</td>
</tr>
<tr>
<td>AIR</td>
<td>Acute Infection of Respiratory Tract Study</td>
</tr>
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<td>ALHS</td>
<td>Adult Lung Health Study</td>
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<td>ART</td>
<td>Antiretroviral Therapy</td>
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<td>ATS</td>
<td>American Thoracic Society</td>
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<td>BHS</td>
<td>Blantyre Health Study</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>BOLD</td>
<td>Burden of Obstructive Lung Disease</td>
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<tr>
<td>CAPS</td>
<td>(The) Cooking And Pneumonia Study</td>
</tr>
<tr>
<td>CAT</td>
<td>COPD Assessment Tool</td>
</tr>
<tr>
<td>CHICAS</td>
<td>Centre for Health Informatics, Computing and Statistics</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CO</td>
<td>Carbon Monoxide</td>
</tr>
<tr>
<td>COMREC</td>
<td>Malawi College of Medicine Research and Ethics Board</td>
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<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
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<tr>
<td>CXR</td>
<td>Chest X-rays (plain)</td>
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<tr>
<td>EMIS</td>
<td>Electronic Medical Information Service</td>
</tr>
<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
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<tr>
<td>FEV₁</td>
<td>Force Expiratory Volume in 1 second</td>
</tr>
<tr>
<td>FVC</td>
<td>Force Vital Capacity</td>
</tr>
<tr>
<td>GACC</td>
<td>Global Alliance for Clean Cookstoves</td>
</tr>
<tr>
<td>GHR</td>
<td>Global Health Research</td>
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<tr>
<td>GLI</td>
<td>Global Lung Initiative</td>
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<tr>
<td>GNI</td>
<td>Gross National Income</td>
</tr>
<tr>
<td>GOLD</td>
<td>Global Initiative for Chronic Obstructive Lung Disease</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner (Medical Doctor in UK)</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HRA</td>
<td>Health Research Authority</td>
</tr>
<tr>
<td>HRCT</td>
<td>High Resolution Computed Tomography</td>
</tr>
<tr>
<td>IAP</td>
<td>Indoor Air Pollution</td>
</tr>
<tr>
<td>ICS</td>
<td>Inhaled Corticosteroid</td>
</tr>
<tr>
<td>IMCI</td>
<td>Integrated Management of Childhood Illness</td>
</tr>
<tr>
<td>IMD</td>
<td>Index of Multiple Deprivation</td>
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<tr>
<td>IQR</td>
<td>Inter-Quartile Range</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
<td>-----------</td>
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<tr>
<td>IRAS</td>
<td>Integrated Research Application System</td>
</tr>
<tr>
<td>ISAAC</td>
<td>International Study of Asthma and Allergies in Childhood</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention- To- Treat</td>
</tr>
<tr>
<td>LABA</td>
<td>Long Acting Beta2 Agonist</td>
</tr>
<tr>
<td>LAMA</td>
<td>Long Acting Muscarinic Antagonist</td>
</tr>
<tr>
<td>LLN</td>
<td>Lower Limits of Normal</td>
</tr>
<tr>
<td>LMIC</td>
<td>Low and Middle Income Countries</td>
</tr>
<tr>
<td>LSTM</td>
<td>Liverpool School of Tropical Medicine</td>
</tr>
<tr>
<td>MDI</td>
<td>Meter Dose Inhaler</td>
</tr>
<tr>
<td>MLW</td>
<td>Malawi-Liverpool-Wellcome Trust (Clinical Research Programme)</td>
</tr>
<tr>
<td>MOH</td>
<td>Ministry of Health (Malawi)</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council (Dyspnoea Scale)</td>
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<tr>
<td>MRC DTP</td>
<td>Medical Research Council Doctoral Training Programme</td>
</tr>
<tr>
<td>NCD</td>
<td>Non-Communicable Disease</td>
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<tr>
<td>NCLD</td>
<td>Non-Communicable Lung Disease</td>
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<tr>
<td>NHS</td>
<td>National Health Service</td>
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<tr>
<td>NIHR</td>
<td>National Institute of Health Research</td>
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<tr>
<td>NTP</td>
<td>National Treatment Programme (Malawi)</td>
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<tr>
<td>ODA</td>
<td>Official Development Assistance</td>
</tr>
<tr>
<td>OPD</td>
<td>Outpatient Department</td>
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<tr>
<td>OR</td>
<td>Odd Ratio</td>
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<tr>
<td>OST</td>
<td>Opiates Substitution Therapy</td>
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<tr>
<td>PEFR</td>
<td>Peak Expiratory Flow Rate</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PM$_{2.5}$</td>
<td>Particulate Matter (equal to or less than 2.5 microns in size)</td>
</tr>
<tr>
<td>PTB</td>
<td>Pulmonary Tuberculosis</td>
</tr>
<tr>
<td>PTLD</td>
<td>Post Tuberculosis Lung Disease</td>
</tr>
<tr>
<td>QECH</td>
<td>Queen Elizabeth Central Hospital (Malawi)</td>
</tr>
<tr>
<td>RR</td>
<td>Risk Ratio</td>
</tr>
<tr>
<td>SABA</td>
<td>Short-Acting Beta$_2$-Agonist</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SE</td>
<td>Standard Error</td>
</tr>
<tr>
<td>SGRQ</td>
<td>St George’s Respiratory Questionnaire</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States (of America)</td>
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<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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Abstract

Chronic respiratory disease affects over 500 million worldwide, with 251 million people suffering from Chronic Obstructive Pulmonary Disease (COPD) causing approximately 3 million deaths a year. In the global North tobacco smoke is known to be a risk factor for COPD, but little is known about the risks of other inhaled substances, such as heroin or the natural history of any respiratory disease associated with it. In the global South there is limited literature describing the burden of chronic respiratory disease or its natural history, with a particular lack of research amongst the more disadvantaged, harder to reach populations in sub-Saharan Africa. These populations have known high risk exposure including biomass use and a high burden of HIV and Tuberculosis. The gap in evidence provides an opportunity to explore the natural history and determinates of three potentially high-risk groups, the first heroin smokers in Liverpool UK, the second users of biomass fuel in rural Malawi, and thirdly those who have completed treatment for tuberculosis (TB) in urban Malawi.

The introduction chapter explains the rationale behind this thesis and highlights the key literature available in each population. The thesis then presents 5 papers, using different methods to explore chronic respiratory disease in these three populations.

The data presented from Liverpool (Study 1: Screening heroin smokers attending community drug clinics for change in lung function: a cohort study) reports heroin users as being at significant risk of COPD. We found that forced expiratory volume in 1 second (FEV₁) declined annually by 90ml (SD 190, p<0.001) which is significantly worse than you would expect in tobacco smokers. In the same population, study 2 (COPD in heroin smokers: a patient perspective) reports that accessing care and correct use of medication was a major problem that needs addressing. In a move from the global North to the global South, I report that the prevalence of chronic respiratory symptoms, spirometric obstruction and restriction in populations using biomass as their main fuel were 13·6% (95% CI:11.9-15.4), 8·7% (95% CI:7·0-10·7) and 34·8% (95% CI:31·7-38·0), respectively (Study 3: Non-communicable respiratory disease and air pollution exposure in Malawi: a cross-sectional study). A systematic review and meta-analysis attempted to estimate the overall burden of chronic respiratory disease in Malawi but noted the heterogeneity of the available data. Airflow obstruction in adults varied between 2.3% and 20% and low FVC between 2.7% and
52.8%. *(Study 4: Non-communicable respiratory disease in Malawi: a systematic review and meta-analysis).* One possible cause of the high levels of abnormal spirometry and respiratory symptoms seen in Malawi could be Post-TB respiratory disease with study 5 *(Respiratory symptoms and lung function in patients treated for pulmonary tuberculosis in Malawi: a prospective cohort study)* highlighting that over a quarter of patients still have abnormal spirometry 3-years after TB-treatment completion. The proportions of participants with low FVC and obstruction changed from 57/285(20.0%) and 41/285(14.4%) at TB treatment completion to 34/272(12.5%) and 43/272(15.8%) at 3-years.

All three populations presented in this thesis live with a significant burden of respiratory disease, often in disadvantaged situations where accessing optimal healthcare can be a challenge. Managing lung health in these populations requires careful planning with further research required into setting appropriate treatment options.
Chapter 1: Introduction

This chapter provides a background and justification of the studies included in this thesis. My research questions, aims, contribution to each study and layout of the thesis are all described.

1.1 Background to this thesis

As a respiratory physiotherapist who has worked and lived both in UK and Kenya, writing a thesis that focused on both the global North and South was important. My host institution, the Liverpool School of Tropical (LSTM) has a similar vision to reach out to disadvantaged populations in its traditional geographical foci in Africa and Asia, and in the UK. I have spent the last 10 years of my career focusing on those that find it hard to access care in their health system or suffer from chronic conditions where accessing care can contribute to the challenges of life. In Kenya I managed the development of a rural health centre into a hospital, working closely with government offices, Non-Governmental Organisations (NGO’s) and other stakeholders to help provide universal healthcare coverage to as many of the poor and less reached rural population as possible. In the UK my work focused on those with chronic respiratory conditions, often working with patients who found attending hospital difficult. This thesis aims to bring together work from the UK and Africa within the overarching theme: chronic respiratory disease in disadvantaged populations. The studies that comprise this thesis took place in three very different locations; Liverpool in the UK, and two contrasting areas in Malawi, urban Blantyre and rural Chikwawa. Despite the geographical differences each location has populations living in conditions of disadvantage and poverty. Such people have significant risk factors for the development of chronic respiratory disease due to their activities (heroin smoking in Liverpool and high biomass use in rural Malawi) or their history of acute respiratory disease (Pulmonary Tuberculosis in Blantyre).

1.2 Drug Users in Liverpool

Liverpool is a city in the North West of the UK, with a population of approximately 500,000 people. Based on the Index of Multiple Deprivation (IMD) scores in 2019 Liverpool was considered the third most deprived local authority out of 317 areas in England, with 49% (145/298) of its lower-layer super output areas (LSOAs) being in the most deprived 10% (1).
According to the Centre for Cities think tank, currently 7.6% of Liverpool City residents claim for unemployment, which may rise due to the current covid-19 pandemic (2).

It is estimated that in 2017 approximately 1% of the total population of the city (4,848) took opiates as an illicit drug, the majority of which was heroin, with 1,895 (409 per 100,000) hospital admissions for drug related mental health or behavioural reason and 205 admission for drug poisoning (40/100,000) in 2019. In 2018 there were 22 “drug related deaths” per 100,000 population in Liverpool City, and 14.3 per 100,000 drug poisoning resulting in death, compared to 6.7 per 100,000 nationally (3). The average age of “in treatment” (those on opiates substitution therapy [OST] therapy ) death in Liverpool being 49 years (4). These figures are some of the highest in country with some press headlines declaring Liverpool as the “Drugs Abuse Capital of England” (5).

1.3 Service available for drug users

Liverpool City has two main providers of drug addiction services. “Mersey Care” provide acute crisis care, and Addaction (recently renamed “We Are With You” but for the purpose of continuity in this thesis will be called Addaction) who are commissioned to provide OST, counselling, job seekers advice, emergency basic supplies and also treatment of related conditions such as hepatitis (6). Addaction works in over 30 GP surgeries, local hubs and community centres across Liverpool City, with an aim to provide an ‘anchor point for drug users to access services’. Heroin smokers often have chaotic lifestyles and engage sporadically with traditional health services, often seeking acute care when unwell but infrequently attending appointments for routine care. Their most consistent, and sometimes only, point of contact with healthcare services is the OST clinic - their ‘anchor point’ (7). Drug users attend weekly, biweekly or monthly appointments with a trained drug counsellor (and a medical professional where needed). A full assessment of their needs is completed at each appointment and a methadone or buprenorphine prescription is provided alongside other care which can range from treatment for hepatitis through to advice on housing issues. The aim is to provide these services close to the clients home address (for example in their GP surgery) and make appointments as accessible and holistic as possible (6). Where the client has no fixed abode, select GP surgeries within Liverpool City deliver a full range of primary care services, and act as a base for these clients. Clients tend to pick up their OST medication daily or weekly at a named local pharmacy which acts
as the second ‘anchor point’ in the care pathway. As it stands, there are no respiratory services provided at these ‘anchor points’ within Liverpool City although other neighbouring local authorities do provide specialist respiratory services at OST clinics (8).

1.4 Smoking of Heroin and the Possible Implication for Lung Health

Over the past three decades increasing numbers of heroin users have moved from injecting heroin intravenously to smoking it (9). Often referred to colloquially as “chasing the dragon”, it has become the preferred route of intake due to the reduced risk of blood-borne diseases such as Human Immunodeficiency Virus (HIV) and Hepatitis C and the lower risk of life-threatening overdose (9, 10). Heroin is normally smoked from aluminium foil, with a cigarette lighter placed under the powder to melt it and the smoke “chased” and inhaled with a straw or pipe (11). Smoking of heroin has been used as a harm reduction method, with drug support charities and public health organisations supplying foil to heroin users, encouraging them away from injecting (12, 13). These have generally been deemed successful with project such as “SMOKE IT” in Germany, resulting in over two-thirds of clients switching from injecting to smoking with reduced risk of HIV, Hepatitis and overdose cited as the reasons for the switch (13).

Until recently there has been little research that focuses on the possible risk associated with smoking heroin. There have been numerous reported cases of acute bronchospasm and acute “asthma” type presentations in heroin smokers. However, there are few data on any ongoing symptoms or chronic disease (14, 15). In 2002 a cross-sectional study of 100 clients using a methadone clinic in Amsterdam found those who smoked heroin had increased odds of dyspnoea and impaired lung function (16). The authors did not report post-bronchodilator spirometry or attempt to diagnose airway disease. Participants were not followed up over time, and therefore it is difficult to make inferences about the nature and progression of the reported chronic respiratory symptoms. More recently it was reported that smoking heroin appears to lead to early onset COPD (diagnosed with spirometry), and a study of 78 individuals in Liverpool described a mean COPD onset age of 41 (17). A cross-sectional screening study of heroin smokers in Liverpool found that 50% of the 753 clients screened had COPD or COPD/Asthma Overlap (18). In 2014 Yadavilli et al. described the hospital admission for patients with chronic obstructive disease, comparing illicit drug smokers to current and ex-tobacco smokers and reported that illicit drug users were
younger (mean age 50 v 72.9/69.9 p<0.001), readmission rates were higher (1.0 v 0.22/0.26 p<0.0001) and requirement for the use of non-invasive ventilation was higher (8.9% in illicit drug users vs. 3% in ever smokers). On average illicit drug users had a shorter hospital stay.

It appears that heroin users do have an increased risk of acute hospital admissions with respiratory disease. However, potentially due to their chaotic lifestyle, it also appears they tend not to present to available primary care facilities (12, 17), possibly leading to an increased burden on the acute hospital system.

Despite the relatively small body of evidence there is growing concern that smoking heroin could lead to an extensive burden of respiratory disease which both significantly impacts the individual and the health systems which they are accessing for care and in 2018 in Liverpool COPD was the most named medical condition in the notes of deceased drug users above hepatitis, liver disease and HIV (4).

1.5 Rationale for the Heroin Users COPD study

To the best of the author’s knowledge there are no studies that investigate the longer term effects of smoking heroin on lung function, the pattern and reasons for the lack of primary health care usage are not fully understood and within Liverpool there have been no studies that specifically investigate the views and opinions of heroin smokers with COPD in relation to their respiratory disease or their access to care.

Objectives:

1. To determine the change in lung function in heroin users with COPD in Liverpool, UK over a 24 month period.

2. To assess the relationship between chronic respiratory disease in heroin smokers and health care usage and treatments.

3. Describe the feasibility of providing screening service at the Addaction ‘anchor points’.

4. Explore the perspective that heroin users have of COPD, treatment and access to care.
1.6 Blantyre and Chikwawa, Malawi

Malawi is located in Eastern Southern Africa and borders Tanzania, Mozambique and Zambia (19). Malawi is home to 18.9 million people, it is a largely rural country and although urban migration is increasing, 80% of employment is still found within agriculture and the majority of families surviving on subsistence farming (19). Although the economy grows by 4.4% in 2019, The Gross national income (GNI) per capita of Malawi is still low $411 compared to UK’s per capita GNI of $42,300 in 2019 (19, 20). Education attainment is low with only 26% of women and 36% of men, enrolling into at least the first year of secondary education (21). Life expectancy has recently improved although it remains relatively low (63.7 years compared 81 years in the UK), with HIV and tuberculosis causing high burden of disease (21).

Blantyre is second largest city in Malawi, with population of 800,000 people, it is a growing city whose population has doubled over the past two decades (22) (figure 1 & 2). Blantyre is the location of the Malawi-Liverpool-Wellcome Trust Clinical Research Programme (MLW) a research facility that houses programmes to prevent death from severe infection, reduce infection transmission, and further understanding of chronic disease and disabilities in Africa (23). MLW works closely with the Queen Elizabeth Central Hospital in Blantyre, one of the countries national referral hospitals with staff often working across the two sites. MLW also has small rural research site in Chikwawa, approximately 50 kilometers from Blantyre in the Southern Shire River Valley. Chikwawa is an area of predominantly rural village communities which engage in

Figure 1 Map of Malawi with Blantyre and Chikwawa highlighted by red circles
subsistence farming (figure 1&3). Both the MLW sites have teams of well-trained nurses and fieldworkers who know the community and are trained to work with in these settings to carry out quality research programmes.

1.7 Lung Health in Malawi

Malawi has a high burden of tuberculosis (TB), with the 2014 national prevalence survey reporting cases of microbiologically confirmed pulmonary TB (PTB) at 452/100,000 and smear positive PTB of 220/100,000, with WHO in 2018 estimating a rate of 181/100,000 (24, 25). In 2018 there were 15,632 reported cases of TB nationally, of which 66% were PTB and 48% had co-infection with HIV(25). Only 126 of the total cases were drug-resistant. There is a well-functioning National TB treatment programme (NTP) within Malawi. Services are decentralised, with treatment registration and monitoring all taking place at a local level with referrals made to QECH only when required. TB diagnosis at local level is normally done using sputum smears. Although there is a move towards rapid Xpert TB/RIF testing being widely available, it is currently only available in larger tertiary hospitals. Diagnosis and treatment is free, with drugs dispensed every 2 weeks. Patients normally must fund their own travel to pick up the medication. In 2017 treatment completion or success (a standard outcome measure in TB treatment) was 86% amongst new and relapsed cases of TB(25) however within the national programme there is little or no follow up of TB after treatment is completed and is deemed a ‘success’.
Until recently very little was known about the general lung health of the population in Malawi with TB and pneumonia being the focus of the countries effort to tackle infectious respiratory disease. In 2017 the Cooking And Pneumonia Study (CAPS) took place in Chikwawa, with the aim of assessing the impact of cleaner-burning biomass fuelled stove on childhood pneumonia(26). Whilst this found that cleaner-burning biomass cookstove had no significant impact on pneumonia in children in Chikwawa, it did highlight a population who were potentially at risk from respiratory disease due to almost exclusive use of biomass as the primary source of fuel for cooking (>99% of households) (26). At a similar time the Burden of Obstructive Lung Disease (BOLD) study was being carried in urban Blantyre. BOLD estimates the prevalence of obstructive disease across 40 countries globally(27) using questionnaires and post bronchodilators spirometry to diagnose respiratory disease and investigate the risk factors associated with it(27). In 2016 it was reported that over 40% of the population had abnormal spirometry when using international spirometry reference ranges (NHANES), and that using weighted (age and sex) prevalence 3.6% had moderate or severe obstruction, with 11.8% reporting they had at least one respiratory symptoms (28). Participants were more likely to have a restrictive spirometry pattern if they had previously had TB (OR, 3.01; 95% CI, 1.07–8.50) (28).

1.8 Post-Tuberculosis Lung Disease

There is a growing body of evidence that patients who are successfully treated for PTB can experience some residual ventilatory abnormalities, with a high burden of both airway obstructive and restrictive disease seen(29-31).

However, despite this there is a lack of evidence that describes the progression and nature of respiratory disease after TB-treatment completion. In a group of South Africa miners it was found that those who had suffered more episodes of PTB had greater lung function deficit: compared with predicted volumes, forced expiratory volume in one second (FEV₁) after one, two, and three or more episodes of tuberculosis was 153 ml, 326 ml, and 410 ml respectively. The greatest function loss occurred within the first six months after diagnosis of PTB(32). A cross sectional comparison of people living with HIV in South Africa demonstrated that participants with a history of PTB had an annual excess loss of lung
function compared to those without a PTB of 35 mL in FEV₁ (95%CI 2–68, p = 0.03) and 57 mL in FVC (95%CI 19–96, p = 0.003) (33). In South Korea in those with spontaneous healed PTB (i.e. healed scars found on chest x-ray as part of survey data) found significantly larger decrease in FEV₁ over 10 years than a control group (33.81ml/year v 31.15ml/year p<0.001)(34). More recently a cohort of post-TB patients were followed in Malawi for 12 months, which reflected data from the South African and South Korean cohorts: there was a high burden of respiratory disease with 60.7% of participants reporting respiratory symptoms and 34.2% having had abnormal spirometry at TB-treatment completion. High-resolution computed tomography (HRCT) also showed 44.2% residual bronchiectasis in at least 1 lobe and 9.4% had a totally destroyed lobe(35). Due to the growing concerns of the impact of lung damage post-TB, the first international post-TB symposium was held in 2019, at which a definition of post-TB lung disease (PTLD) was agreed as: “Evidence of chronic respiratory abnormality, with or without symptoms, attributable at least in part to previous pulmonary tuberculosis” (36). Despite this definition it was also clear that further research is needed into the progression of PTLD over time, with no literature found that documents lung function and change in symptoms over time after 12-months in a cohort of PTB survivors.

1.9 Rationale for Lung Health in Rural Malawi and Post-TB Studies

To the best of the author’s knowledge there are no studies that review the burden of respiratory disease in rural Malawi, particularly in the context of known high biomass usage. There are also no studies that systematically review the literature to assess the burden of chronic respiratory disease within Malawi. Thirdly there are no existing data on the longer-term outcomes associated with PTB in Malawi.

Objectives

1. To report the prevalence of spirometric abnormality in rural Malawi (Chikwawa) and the associated risk factors including household air pollution
2. To estimate the burden of chronic disease in Malawi by conducting a systematic review and meta-analysis of available data
3. To report change in lung function in the 3 years following completion of TB-treatment, and risk factors for decline.
1.10 Thesis Hypothesis

Those living in disadvantaged situations and exposed to possible high-risk activities or disease (heroin smoke, biomass fuel and TB) could have increased burden of respiratory disease, as measured by symptoms and spirometry.

1.11 Structure of Thesis

This thesis is presented by paper. Each paper has been presented as a standalone chapter with a summary introduction and a full explanation of the contributions of myself and co-authors to the published manuscripts. This thesis is constructed according to the LSTM guidelines, which mandate that each paper is presented in Microsoft Word format as it was accepted by the journals but with reference numbers that fit with overall structure of this thesis. PDF copies of each paper are presented in the Appendices.

Chapter 1: A description of the thesis as a scene setting. This includes a brief introduction to the literature and reasons for each of the five studies.

Chapter 2: The first paper, screening heroin smokers attending community drug clinics for change in lung function: a cohort study. This study is the first novel work of the thesis and describes the lung function change over time in a group of heroin users.


Chapter 3: Exploring perspectives on chronic obstructive pulmonary disease in people who smoke heroin: a qualitative study. This chapter gives more insight into the challenges facing heroin users with COPD, with an aim to giving a human voice to complement the quantitative description in Chapter 2.

Chapter 4: In a move from Liverpool to Malawi, I report the burden respiratory disease seen in Chikwawa. Noncommunicable Respiratory Disease and Air Pollution Exposure in Malawi (CAPS). A Cross-Sectional Study


Chapter 5: Moving in from Chikwawa to Malawi as a whole, I attempt to describe the burden of chronic respiratory disease by conducting and systematic review and meta-analysis. Non-communicable respiratory disease in Malawi: a systematic review and meta-analysis.


Chapter 6: Given the finding of previous TB disease as a possible determinant of lung function in Malawi and sub-Saharan Africa, in this final paper of thesis I describe the lung function change in post-PTB 3 years after TB-treatment completion. Respiratory symptoms and lung function in patients treated for pulmonary tuberculosis in Malawi: A prospective cohort study.


Chapter 7: Is a general discussion that draw together the findings of the studies an outlines possible further research and implications for policy.
1.12 References


Chapter 2: Screening Heroin Smokers Attending Community Drug Clinics for Change in Lung Function: a Cohort Study

2.1 Chapter Layout

This chapter is presented as it was accepted for publication, but before typesetting. For ease of reading I have included the tables and figures in the text. When this was submitted, the table and figures were presented as a separate document. I have labelled each section 2. ‘X’ for indexing. The PDF of the paper can be found in the Appendix for chapter 2 section 1. The supplement can be found in the Appendix for chapter 2 section 2.

2.2 My Contribution to the Paper

This paper comprises two parts; the baseline initial data collection and the follow up. The baseline data was collected for a service evaluation conducted by Dr Hassan Burhan. I was Principal Investigator (PI) for the follow up, and as the primary applicant sought and received permissions from the Research Integrated Application System (IRAS), Addaction and LSTM (the sponsor). I wrote the study protocol and all data collection tools used. I set up the master file and completed or supervised all the administrative tasks to allow this research to take place. I carried out all the data collection at every site for this follow up study, including carrying out and interpreting the spirometry. Hospital inpatient data was collected by a member of the respiratory team according to a data capture tool which I created. I cleaned and analysed the data, including all coding in Stata and R. I received support from supervisors Dr Emanuele Giorgi and Dr Jamie Rylance who provided advice on the final model used in this paper. Although for logistical reasons Dr Jamie Rylance was corresponding author, I wrote the first draft of this paper, co-ordinated edits from other authors and I wrote and edited the responses to reviewer criticism before publication.

2.3 Contribution of other authors to the paper

<table>
<thead>
<tr>
<th>Name</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof Kevin Mortimer</td>
<td>Second PhD supervisor, read draft and commented.</td>
</tr>
<tr>
<td>Dr Emanuele Giorgi</td>
<td>Provided statistical modelling support and was my MRC DTP Lancaster PhD supervisor</td>
</tr>
<tr>
<td>Dr Paul Walker</td>
<td>Involved in baseline data collection, read draft and commented</td>
</tr>
<tr>
<td>Dr Marie Stolbrink</td>
<td>Collected hospital data according the protocol and read final draft and commented</td>
</tr>
<tr>
<td>Name</td>
<td>Contribution</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ms Tara Byre</td>
<td>Co-ordinator for Addaction, including helping to book patients and brief keyworkers on the study.</td>
</tr>
<tr>
<td>Ms Kerry Marwood</td>
<td>Keyworker for COPD at Addaction, help plan site visit, book patients and explain the patient information sheet. Provided a link between myself and the client. She or another keyworker were present for all visits.</td>
</tr>
<tr>
<td>Dr Sally Morrison-Griffiths</td>
<td>Provided medical supervision for Addaction, involved in the baseline data collection, read and comment on the draft paper.</td>
</tr>
<tr>
<td>Ms Susan Renwick</td>
<td>Involved in the baseline data collection, provided commissioners oversight on the service being provided to this vulnerable group. Read and comment on the final draft of the paper.</td>
</tr>
<tr>
<td>Dr Jamie Rylance</td>
<td>Primary PhD supervisor. Provided support at all stages including reading drafts ethics, protocols and this final paper. Provided overall senior support with Dr Burhan.</td>
</tr>
<tr>
<td>Dr Hassan Burhan</td>
<td>Joint senior author with Dr Jamie Rylance, Dr Burhan was first name author on the published baseline data. He double read all spirometry traces with me for this paper, provide Doctors coverage for the study and read and commented on the final draft of the paper.</td>
</tr>
</tbody>
</table>

### 2.4 This Paper as Part of the Thesis

This is the first paper of this thesis. In Liverpool, UK, data collection took place at the same time as participants picked up their methadone or buprenorphine prescriptions. The manuscript describes a longitudinal study to investigate change in lung function in heroin users with COPD in Liverpool over a 24-month period. It also assesses the relationship between chronic respiratory disease in heroin smokers and possible risk factors such as smoking tobacco and healthcare usage. It was also a preliminary test of feasibility for holding respiratory clinics at OST sites. In the context of the wider thesis, this paper is the first of three papers that aim to assess lung function in disadvantaged populations, and one of two papers that follow-up cohorts of patients over time. It provides insight into progression of COPD in heroin smokers which together with findings from chapter 3 provides data to guide future commissioning of health services for this population in Liverpool.
2.5 Title Page

Screening heroin smokers attending community drug clinics for change in lung function: A cohort study

Authors

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7 Royal Liverpool and Broadgreen University Hospitals, Liverpool, UK

Short title

Lung function decline in inhaled drug users

Author contributions

Design: RN,KM, TB, SMG, PPW, SR, JR, HB
Acquisition of data: RN, KM, MS, TB, SMG, HB
Analysis of data: RN, EG, JR, HB
Interpretation of data: RN, KM, JR, HB
Writing the manuscript, approval of the version to be published and agreement to be accountable for all aspects of the work: All authors

Funding

This project was funding by the medical research council doctoral training programme. (MRC DTP). Liverpool Clinical Commissioning Group funded the baseline data collection
and a Health Foundation charity grant assisted with administrative support for repeat spirometry.
2.6 Abstract

**Background:** Heroin smokers have high rates of chronic obstructive pulmonary disease (COPD), respiratory morbidity, hospital admission and mortality. We assessed the natural history of symptoms and lung function in this population over time.

**Methods:** A cohort of heroin smokers with COPD was followed for 18-24 months. At baseline and follow-up, respiratory symptoms were measured by Medical Research Council Dyspnoea Scale (MRC) and COPD Assessment Tool (CAT), and post-bronchodilator spirometry was performed. Frequency of healthcare-seeking episodes was extracted from routine health records. Parametric, non-parametric and linear regression models were used to analyse the change in symptoms and lung function over time.

**Results:** Of 372 participants originally recruited, 161 were assessed at follow-up (mean age 51.0 [SD 5.3], 74 [46%] female) and 106 participants completed post bronchodilator spirometry. All participants were current or previous heroin smokers and 122 (75.8%) had smoked crack. Symptoms increased over time (MRC score increased 0.48 points per year, p<0.001; and CAT score increased by 1.60 points per year, p<0.001). Forced expiratory volume in 1 second (FEV₁) declined annually by 90ml (SD 190, p<0.001). This deterioration was not associated with change in tobacco or heroin smoking status or use of inhaled medications.

**Conclusion:** Heroin smokers experience a high and increasing burden of chronic respiratory symptoms, and a decline in FEV₁ that exceeds the normal age-related decline observed amongst tobacco smokers with COPD and healthy non-smokers. Targeted COPD diagnostic and treatment services hosted within opiate substitution services could benefit this vulnerable, relatively inaccessible, and underserved group of people.
2.7 Introduction

Illicit drug use is common, with 8.5% of adults in England and Wales having reported taking an illicit drug in 2016/2017 [1]. Over the last thirty years smoking rather than injecting heroin has become more common [2-6]. In recent years smoking heroin rather than injecting has been used as a possible method of harm reduction[7, 8].

Although the effects of illicit drug use are well documented, there is limited evidence about the chronic effects of inhaled illicit drug use on the respiratory system. Multiple case reports highlight acute asthma attacks in heroin users, and observational studies report a high prevalence of respiratory disease in heroin users admitted to acute hospitals [9, 10]. Severe early onset emphysema associated with premature mortality has been reported among heroin users [11-13]. However large-scale diagnostic studies in this hard-to-reach population are lacking. Chronic respiratory symptoms are common in those inhaling heroin, yet access to formal diagnosis including lung function measurement is limited [14-16].

We recently reported post bronchodilator spirometry in 703 heroin smokers attending for opiate substitution therapy (OST) at community drug service clinics in Liverpool; 50% of heroin smokers had either COPD or COPD-asthma overlap (ACO) despite a mean age of 47 years [17]. This was associated with extensive respiratory symptoms, which given the known high rates of COPD hospitalisation and a continuing trend towards inhalation as the mode of drug use is likely to put increased burden on health systems [4, 6, 18]. In light of this, screening and treatment programmes for heroin smokers could be a viable method for identifying and treating disease in this relatively inaccessible patient group [19].

We performed a longitudinal cohort study of heroin smokers attending community drug services and who were recruited as an original cohort of 703 heroin smokers described in terms of baseline characteristics in our previous paper [17]. The aim was to ascertain their change in health status, respiratory symptoms and lung function over an 18-24 month period.
2.8 Methods

Setting

The study was performed in 31 community drug service clinics in Liverpool, UK. Clinics are run by Addaction, a large independent charity commissioned by the local city council public health department. A keyworker who knew the client and who coordinated their OST worked with the study team in each clinic.

Participants

Participants were invited to take part if they had previously completed spirometry in the baseline screening project that took place between December 2015 and June 2016[17], were over the age of 18 years, and were still fully enrolled in Addaction’s service. All participants were current or previous smokers of heroin and were currently or recently treated with methadone or buprenorphine. Participants were given the study information prior to being booked for their regular appointment and were offered a study visit at their usual clinic. Those missing their usual appointment were offered another at a central venue. Written informed consent was obtained from all participants.

Variables and Data Source

Baseline data collection has been previously described [17]. In brief, participants completed a questionnaire detailing demographic data, and self-reported tobacco and illicit drug use. Oxygen saturations were measured, and pre-and post-bronchodilator spirometry was completed.

At follow up participants completed a questionnaire which evaluated self-reporting medication prescriptions, health care access, and ongoing tobacco and illicit drug use. The index of multiple deprivation (IMD), which is an official geographic measure of relative deprivation in England was used a proxy of social-economic status [20]. Participants also completed the COPD assessment tool (CAT) [21] and the Medical Research Council (MRC) dyspnoea scale [22], and consented to allow review of 2 years of medical records for respiratory related diagnosis and prescriptions from primary care pharmacy records (EMIS), and hospital records where applicable.
Oxygen saturations were measured, and pre-and post-bronchodilator spirometry was performed on all participants who consented and did not have medical contraindications. Spirometry was performed by trained clinical staff and completed according to American Thoracic Society (ATS) guidelines [23]. All traces were double-reviewed for quality and grading by an experienced respiratory physician. As with the baseline survey, participants were asked not to take a short acting bronchodilator within 8 hours of visit or a long-acting bronchodilator within 24 hours. If they had taken a short acting inhaler, only post bronchodilator spirometry was recorded.

Subjects were categorised based on original screening. A diagnosis of asthma was given if airflow obstruction (Forced Vital Capacity /Forced Vital Capacity (FEV₁/FVC) ratio <0.7) was fully reversible to inhaled salbutamol i.e. either FEV₁/FVC normalised or FEV₁ increased by ≥400ml, or if spirometry was normal but the participant had a prior physician diagnosis of asthma. Those with non-reversible airflow obstruction were characterised as COPD unless they had a prior physician diagnosis of asthma, in which case their condition was labelled asthma-COPD overlap (ACO). We report the lung function change of those participants who had been diagnosed with COPD or ACO at baseline, those with an asthma diagnosis were excluded [17].

All spirometry data was reported using the European Community for Steel and Coal reference ranges for consistency with prior work [24]. Abnormal spirometry was defined using Global Initiative for Chronic Obstructive Lung Disease (GOLD) [25]. Change in lung function was based on post-bronchodilator FEV₁.

**Sample Size**

We aimed to follow up as many of the participants with COPD or ACO from baseline as possible.

**Statistical analysis**

Univariate analysis was carried out using descriptive statistics to explore the characteristics of the study populations. Paired t-tests and Wilcoxon sign rank tests (with bootstrapping to estimate the confidence interval of the difference) were used to assess change between the two time points. Time was used as a continuous variable to account for variation between
follow ups dates and to calculate an annualised change). A linear regression model was used to estimate the effect of potential factors (change in inhaled illicit drug use, change in tobacco smoking, change in inhaler use) on changes in FEV₁ over time. Variables were selected for the model a priori based on clinical data which might have varied over the course of follow-up within an individual, specifically those which described changes in drug or medication use. The whole model is presented without variable elimination. Data were analysed using Stata version 14.2 statistical software and R version 3.4 (R Foundation for Statistical Computing). Statistical significance was tested at the conventional 5% level.

**Ethics**

Ethical approval was gained from Health Research Authority (HRA) via the integrated Research Application System (IRAS) number: 235151
2.9 Results

A total of 372 participants had previous COPD or ACO and were eligible for inclusion. The study follow-up took place between December 2017 to April 2018. Baseline questionnaire and clinical data were collected from 161 participants; 109 were lost to follow up, 49 did not attend the follow up appointment, 26 declined at the appointment, 23 were medically unfit and four did not take part for other reasons. 106 completed post-bronchodilator spirometry at both baseline and follow-up to ATS standards. Those remaining (n=55) did not meet ATS standards (22), were medical unfit (3), died (1) or declined post-bronchodilator spirometry (29) (Figure 1). Compression of participants characteristics can be seen in table E1 (appendix section 2).

Figure 1 Flow of participants through the study

<table>
<thead>
<tr>
<th>372 service users had previous diagnosed COPD or ACO and they:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Were receiving a prescription for methadone or buprenorphine</td>
</tr>
<tr>
<td>2) Were under shared care between GP and drug service provider</td>
</tr>
<tr>
<td>3) Had previous spirometry with drug service provider since 2015</td>
</tr>
</tbody>
</table>

| 263 had connected with their key worker and agreed to consider participation |
| 161 consented to participate and met the inclusion criteria |
| 161 completed |
| 1 died |
| 29 declined post bronchodilator spirometry |
| 3 medically unfit |
| 106 had baseline and follow up post bronchodilator spirometry |

| 49 did not attend the appointment |
| 26 declined at the appointment |
| 23 were medically unfit |
| 1 did not meet inclusion criteria |
| 3 did not consent for other reasons |

| 22 failed to achieve post bronchodilator to ATS standard, declined or only completed pre - bronchodilator spirometry |
The characteristics of the population are given in Table 1. Participants had a mean (SD) age of 51 (5.3) years, and 46 (28.6%) were female. The majority of participants were unemployed with high levels of socioeconomic deprivation (mean IMD score 51.5 is in the lowest quintile for the England). All participants were taking OST with 76 (47.2%) reporting current heroin use.

Most were both prescribed an inhaler and were collecting prescriptions (defined as at least 50% pick up rate), from a pharmacy. (n=131 ; 81.4%). No inhalers were prescribed or collected for 21 participants (13.3%), and data were unavailable for 9 participants (5.5%). Of those where data were available 129 (84.9%), 88 (57.9%) and 78 (51.3%) collected prescriptions for short-acting beta_2-agonist (SABA), long acting muscarinic antagonist (LAMA) and an inhaled corticosteroid/long acting beta_2 agonist combination, respectively (Figure 2). Three-quarters had attended a primary care practitioner for respiratory complaints within the preceding 2-years, with 18 (11%) requiring admission to hospital, staying for a mean 11.5 days. Those admitted to hospital were universally treated with bronchodilators, antibiotics and steroids, three participants were offered non-invasive ventilation, two were treated in high-dependency areas and none had level-3 care (invasive ventilation) (Table 2).
Table 1: Characteristics of those 161 people with baseline COPD or ACO derived from follow up questionnaire data.

<table>
<thead>
<tr>
<th></th>
<th>n=161</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n female (%)</strong></td>
<td>46 (28.6)</td>
</tr>
<tr>
<td><strong>Age in years, mean (SD)</strong></td>
<td>51.0 (5.3)</td>
</tr>
<tr>
<td><strong>IMD Score</strong></td>
<td>51.5 (12.7)</td>
</tr>
<tr>
<td><strong>Occupation</strong></td>
<td></td>
</tr>
<tr>
<td>Unemployed, n (%)</td>
<td>137 (85.1)</td>
</tr>
<tr>
<td>Employment, n (%)</td>
<td>24 (14.9)</td>
</tr>
<tr>
<td><strong>Housing</strong></td>
<td></td>
</tr>
<tr>
<td>Own home (including rented), n (%)</td>
<td>124 (77.0)</td>
</tr>
<tr>
<td>Homeless, n (%)</td>
<td>6 (3.7)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>31 (19.3)</td>
</tr>
<tr>
<td><strong>Cigarette Smoking Status</strong></td>
<td></td>
</tr>
<tr>
<td>Current, n (%)</td>
<td>133 (82.6)</td>
</tr>
<tr>
<td>Ex, n (%)</td>
<td>27 (16.8)</td>
</tr>
<tr>
<td>Never, n (%)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td><strong>Cigarettes smoked per day/ SD</strong></td>
<td>11 (7.0)</td>
</tr>
<tr>
<td><strong>Heroin Smoking Status</strong></td>
<td></td>
</tr>
<tr>
<td>Current, n (%)</td>
<td>76 (47.2)</td>
</tr>
<tr>
<td>Ex, n (%)</td>
<td>85 (52.8)</td>
</tr>
<tr>
<td><em><em>Bags smoked per week</em>, n (SD)</em>*</td>
<td>4.0 (7.0)</td>
</tr>
<tr>
<td><strong>Crack smoking</strong></td>
<td></td>
</tr>
<tr>
<td>Current, n (%)</td>
<td>33 (20.5)</td>
</tr>
<tr>
<td>Ex, n (%)</td>
<td>89 (55.3)</td>
</tr>
<tr>
<td>Never, n (%)</td>
<td>39 (24.2)</td>
</tr>
<tr>
<td><strong>Rocks smoked per week, n (SD)</strong></td>
<td>2.18 (1.4)</td>
</tr>
<tr>
<td><strong>Cannabis Smoking Status</strong></td>
<td></td>
</tr>
<tr>
<td>Current, n (%)</td>
<td>38 (23.8)</td>
</tr>
<tr>
<td>Ex, n (%)</td>
<td>53 (33.1)</td>
</tr>
<tr>
<td>Never, n (%)</td>
<td>69 (43.1)</td>
</tr>
<tr>
<td><strong>Cannabis joint per week, n (SD)</strong></td>
<td>12 (17.1)</td>
</tr>
<tr>
<td><strong>Ever injected Heroin, n (%)</strong></td>
<td>30 (18.5)</td>
</tr>
<tr>
<td><strong>Current Methadone dosage, mean mL/day (SD)</strong></td>
<td>45.7 (21.6)</td>
</tr>
<tr>
<td><strong>Current buprenorphine dosage, mean mg/day (SD)</strong></td>
<td>10.4 (8.8)</td>
</tr>
</tbody>
</table>

* a bag is estimated to equate to 0.1g
Participants prescribed and picking up their inhalers (at least 50% of what was expected as recorded by the pharmacy team) as recorded on the primary care electronic prescribing system. Inhalers reviewed were Short Acting Beta2 Agonist (SABA), Long Acting Beta2 Agonist (LABA), Long Acting Anti-Muscarinic (LAMA) and Inhaled Corticosteroid (ICS).

Table 2: Healthcare utilisation from 2 years prior to follow up, amongst those who completed follow up questionnaires.

<table>
<thead>
<tr>
<th>Health Outcome</th>
<th>n=161</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taking an inhaler regularly</td>
<td></td>
</tr>
<tr>
<td>Yes, n (%)</td>
<td>131 (81.4)</td>
</tr>
<tr>
<td>No, n (%)</td>
<td>21 (13.0)</td>
</tr>
<tr>
<td>Not known, n (%)</td>
<td>9 (5.6)</td>
</tr>
<tr>
<td>Reported GP visits in last 2 years for respiratory conditions</td>
<td></td>
</tr>
<tr>
<td>Yes, n (%)</td>
<td>121 (75.2)</td>
</tr>
<tr>
<td>No, n (%)</td>
<td>25 (15.5)</td>
</tr>
<tr>
<td>Not known, n (%)</td>
<td>15 (9.3)</td>
</tr>
<tr>
<td>Number Primary care visit (GP or Nurse), mean (SD)</td>
<td>8.6 (7.0)</td>
</tr>
<tr>
<td>Emergency hospital visits for respiratory conditions</td>
<td></td>
</tr>
<tr>
<td>Yes, n (%)</td>
<td>17 (10.6)</td>
</tr>
<tr>
<td>No, n (%)</td>
<td>114 (70.8)</td>
</tr>
<tr>
<td>Not known, n (%)</td>
<td>30 (18.6)</td>
</tr>
<tr>
<td>Emergency hospital visits of those who did attend, mean (SD)</td>
<td>2.6 (1.9)</td>
</tr>
<tr>
<td>Admitted to hospital in last 2 years for respiratory conditions</td>
<td></td>
</tr>
<tr>
<td>Yes, n (%)</td>
<td>17 (10.5)</td>
</tr>
<tr>
<td>No, n (%)</td>
<td>121 (74.7)</td>
</tr>
<tr>
<td>Not known, n (%)</td>
<td>24 (14.8)</td>
</tr>
<tr>
<td>Length of hospital stay, mean days (SD)</td>
<td>11.5 (13.0)</td>
</tr>
</tbody>
</table>

*Data was gathered from electronic medical records; participants not appearing on these systems are coded as “Not known”, but might engage with extra-regional, informal or private healthcare providers.
The mean FEV$_1$ was 2.05L (SD 0.96) at follow up compared to 2.23 (SD 0.97) at baseline. Of those diagnosed with COPD/ACO at baseline and post-bronchodilator spirometry at both time points, 94 (88.7%) had spirometry indicative of COPD at follow up, with 38 (35.9%) having severe or very severe COPD (using GOLD guidelines) at follow-up compared to 26 (24.6%) at baseline. A further 5 (4.7%) had full reversibility (over 400 ml) and therefore were diagnosed with asthma and 7 (6.6%) had normal spirometry at follow up (Table 3).

Participants reported a significant annualised increase in respiratory symptoms with the MRC and CAT scores increasing by a median of 0.48 (p<0.001) and 1.60 (p<0.001), respectively. They experienced a significant annualised decline in FEV$_1$ and median oxygen saturation of 90ml (p<0.001) and 0.92% (p<0.001), respectively (table 4). Change in smoking status and inhalers use were pre-hypothesised possible clinical factors that could influence FEV$_1$ change. Since baseline, 49 (31.2%) participants reported a decrease in heroin smoking, and 73 (46.5%) reporting an unchanged usage (Figure 3). Change in drug use was not associated with change in FEV$_1$. The final model showing change in drug and tobacco smoking status and inhaler use is presented in Table 5.

Table 3 Diagnosis and post-bronchodilator spirometry at baseline and 2-year follow-up of the 106 participants diagnosed with COPD or ACO at baseline who completed follow-up

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV$_1$, mean L (SD)</td>
<td>2.23 (0.97)</td>
<td>2.05 (0.95)</td>
</tr>
<tr>
<td>FEV$_1$, % predicted (SD)</td>
<td>69.1 (2.6)</td>
<td>64.6 (2.7)</td>
</tr>
<tr>
<td>FVC, mean L (SD)</td>
<td>4.07 (1.2)</td>
<td>3.69 (1.1)</td>
</tr>
<tr>
<td>FVC, % predicted (SD)</td>
<td>102.7 (23.7)</td>
<td>95.5 (23.4)</td>
</tr>
<tr>
<td>FEV$_1$/FVC, ratio (SD)</td>
<td>0.54 (0.13)</td>
<td>0.53 (0.14)</td>
</tr>
</tbody>
</table>

Diagnosis (GOLD)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ACO, n (%)</td>
<td>4 (3.8)</td>
</tr>
<tr>
<td>Asthma, n (%)</td>
<td>-</td>
</tr>
<tr>
<td>Normal, n (%)</td>
<td>5 (4.7)</td>
</tr>
</tbody>
</table>

Severity (GOLD)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild, n (%)</td>
<td>37 (34.9)</td>
</tr>
<tr>
<td>Moderate, n (%)</td>
<td>39 (36.8)</td>
</tr>
<tr>
<td>Severe, n (%), n (%)</td>
<td>15 (14.2)</td>
</tr>
<tr>
<td>Very Severe, n (%)</td>
<td>11 (10.4)</td>
</tr>
</tbody>
</table>
Table 4 Annualised change in spirometry and symptoms in the 106 participants diagnosed with COPD or ACO at baseline who completed follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Follow up</th>
<th>Change per year</th>
<th>Bootstrapping CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV₁ L, mean (SD)</strong></td>
<td>2.23 (97.12)</td>
<td>2.05 (95.60)</td>
<td>-0.09 (0.19)</td>
<td>-0.05--0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MRC Score, median (P25-P75)</td>
<td>3 (2-4)</td>
<td>4 (3-5)</td>
<td>0.46 (0.0-1.0)</td>
<td>0.52 (0.36-0.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAT Score, median (P25-P75)</td>
<td>25 (17-31)</td>
<td>29 (23-33)</td>
<td>1.60 (-0.48-4.32)</td>
<td>0.46 (0.29-0.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SpO₂ (%), median (P25-P75)</td>
<td>97 (96-98)</td>
<td>95 (93-96)</td>
<td>-0.92 (-1.63-0.0)</td>
<td>0.53 (0.38-0.66)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*FEV: Force vital capacity in 1 second, MRC Medical Research Council Dyspnoea score, CAT COPD Assessment Test, SPO2 Peripheral Capillary Oxygen Saturation*

Figure 3 Change in daily consumption of tobacco, heroin and crack in 161 subjects over 2 years

*If they have never smoked their smoking status was recorded as “stayed the same”.*
Table 5 Linear Regression Model of post bronchodilator FEV$_1$ change (n=106).

<table>
<thead>
<tr>
<th>Change in reported heroin consumption</th>
<th>Coefficient (95% CI) for FEV$_1$ decrease (ml/year)</th>
<th>p-value (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Increase*</td>
<td>5.92 (3.46-15.31)</td>
<td>0.36 (95%)</td>
</tr>
<tr>
<td>Decrease†</td>
<td>5.35 (-6.31-17.03)</td>
<td>0.21 (95%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change in reported crack consumption</th>
<th>Coefficient (95% CI) for FEV$_1$ decrease (ml/year)</th>
<th>p-value (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Increase*</td>
<td>0.18 (-9.00-7.68)</td>
<td>0.96 (95%)</td>
</tr>
<tr>
<td>Decrease†</td>
<td>2.69 (-10.55-15.94)</td>
<td>0.69 (95%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change in tobacco consumption</th>
<th>Coefficient (95% CI) for FEV$_1$ decrease (ml/year)</th>
<th>p-value (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Increase*</td>
<td>7.81 (-9.91-7.68)</td>
<td>0.80 (95%)</td>
</tr>
<tr>
<td>Decrease†</td>
<td>-1.11 (-8.51-24.14)</td>
<td>0.34 (95%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change in inhaler use</th>
<th>Coefficient (95% CI) for FEV$_1$ decrease (ml/year)</th>
<th>p-value (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase*</td>
<td>-3.20 (-12.12-5.72)</td>
<td>0.48 (95%)</td>
</tr>
<tr>
<td>Decrease†</td>
<td>1.79 (-11.61-15.20)</td>
<td>0.79 (95%)</td>
</tr>
</tbody>
</table>

* A positive change is an increase in use since baseline, † A negative change is a decrease in usage since baseline.

2.10 Discussion

In a population of heroin smokers we found a high burden of lung disease. In the previously published baseline data 50% of heroin users had COPD or ACO, with a mean MRC of 3.1 and CAT score of 22.9 [17]. At follow-up participants’ respiratory symptoms had worsened significantly from baseline, with annual increases in both CAT score (1.60) and MRC score (0.46), and mean oxygen saturation dropping from 97% to 95% from baseline to follow up.

We found that lung function measured by FEV$_1$ declined by 90ml annually, which was both statistically and clinically significant. The proportion of subjects classified as having severe or very severe disease with this rising from 25% to 36% over the 2-year follow up period.

Neither ongoing illicit drug use nor prescriptions of inhaled medication were associated with change in lung function.

The symptoms reported in this study are consistent with those of studies in this population, with increased dyspnoea amongst heroin users being the common symptom [12, 13, 27]. The decline in health status measured by a CAT score increase of 1.60 annually, is greater than 1 unit change seen in stable COPD patients[26]. The rate of decline in FEV$_1$ is considerably higher than both the 30ml/year age-related decline seen in non-smokers and
in people with tobacco-related COPD (which is reported at 35-79ml per year, of which all but one paper reported an annual decline of 69ml or less) [27, 28]. To date research on lung function in heroin smokers has focused on cross-sectional studies. The results from this longitudinal cohort study support and enhance previous cross-sectional studies that suggested heroin users are at a high risk of COPD and suggests that their decline is worse than that of tobacco smokers. Walker et al found heroin smokers developed early onset emphysema, with a mean age of diagnosis being 41 years, suggesting likely early progression of disease compared to non-heroin smokers [11]. In Amsterdam, Buster et al reported difference in FEV₁ from predicted values, finding that heroin smokers had a FEV₁ of 260ml less than predicted FEV₁ [14].

The rapid decline in FEV₁ and the increase in respiratory symptoms in this population suggests heroin smoking is a driver of decline in lung function. Similarly, once established this decline appears to continue even in those who stop smoking drugs.

Although COPD hospital admissions vary greatly across the UK, those with COPD tend to have high health care usage, particularly in areas of high deprivation [29, 30]. Previous research has also shown that heroin users with respiratory exacerbations are more likely to be readmitted with exacerbations than current / ex-tobacco smokers (OR: 1.00 versus 0.22/0.26) [18]. It is also clear that with high levels of health care access observed in this population, it is likely that ongoing trends towards inhaling heroin will further increase the use of, and burden on, the health system [4, 6].

Strengths of our study include that we followed up the participants over a 18-24 month period, in a community clinic setting. We have shown that it is feasible to engage this client group in both baseline and follow up spirometry allowing for a diagnosis to be made. The lost to follow up rate is a major limitation of this study, reducing the power of statistical analysis and makes stratification of our results by age or GOLD stage unfeasible. Given a larger group, this information would potentially be helpful for targeting care, and is an area for future investigation. This population tends to smoke a mix of heroin, crack and tobacco, establishing a causal relationship is therefore difficult. The participants in the study were generally from a poor socio-economic background, and there is potential that their living condition environment could contribute to the rate of decline. Without significant heterogeneity of such potentially confounding factors, we have been unable to address this
question further. There is also potential for selection bias, with those who regularly attend methadone clinics and have concerns about their respiratory system more likely to participate in the study.

In summary, our findings show the significant respiratory impairment with which heroin smoking is implicated, and a concerning accelerated rate of decline over time. Future studies with larger cohorts, possibly in the context of a targeted public health intervention, are needed to understand if specific sub-groups are especially vulnerable, and how the personal and healthcare costs associated with chronic respiratory illness could be best averted. The study methodology is in support of it being feasible to co-locate respiratory and drug services to one community location. Future studies may benefit from a parallel group of heroin users without spirometric abnormalities at baseline to determine their rate decline compared to those with COPD. These results combined with previous studies support the call for enhanced screening for inhaled drug users [19]. A pilot followed by clinical trial would be needed to assess if screening and treatment services would be clinically and cost effective in this population.
2.11 References

Chapter 3: COPD in Heroin Smokers: a Patient Perspective

3.1 Chapter Layout

This chapter is presented as a copy of the Word document as it was accepted for publication. The only change is that sections have been labelled 3.'X' for easy of indexing. This includes a number of edits made by the journal editors during pre-publication: some of the quotes are redacted or paraphrased (indicated by square parentheses) to remove explicit language and to remove the full description of how to repurpose an inhaler as a drug pipe. The PDF of this paper can be found in the Appendix for Chapter 3 Section 1, and the supplemental information in Section 2.

3.2 My Contribution to the Paper

I was Principal Investigator (PI) on this research project. I wrote all the study protocols, interview topic guides and research and governance applications to IRAS, Addaction (the host organisation) and LSTM (the sponsor). The interviews were carried out by an experienced doctor with an in-depth knowledge of COPD (Dr Paul Griffiths). I trained the interviewer to perform qualitative interviews and reviewed the primary data. I wrote the topic guide, designed the data analysis framework and performed the initial analysis. All transcripts were dual read by myself and Dr Griffiths, and I led the decisions during thematic analysis. Themes were circulated to other authors to ensure consensus, but I was responsible for the final coding and choosing representative illustrative quotations. I drafted the manuscript, performed all subsequent editing, and acted as corresponding author.

3.3 Contribution of Other Authors to the Paper

<table>
<thead>
<tr>
<th>Name</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Paul Griffiths</td>
<td>Conducted the interviews and acting as the second reviewer/opinion on deciding the themes and codes.</td>
</tr>
<tr>
<td>Prof Kevin Mortimer</td>
<td>UK based PhD supervisor, read and comment on drafts</td>
</tr>
<tr>
<td>Dr Paul Walker</td>
<td>Involved in the original quantitative baseline data collection (chapter 2), read draft and commented</td>
</tr>
<tr>
<td>Ms Tara Byre</td>
<td>Co-ordinator for Addaction, including helping to book patients and brief keyworkers on the study.</td>
</tr>
<tr>
<td>Ms Kerry Marwood</td>
<td>Keyworker for COPD at Addaction, helped plan site visits, book patients and explain the patient information sheet. Provided a link between myself and the client. She or another keyworker were present for all visits.</td>
</tr>
<tr>
<td>Name</td>
<td>Contribution</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dr Sally Morrison-Griffiths</td>
<td>Provided medical supervision for Addaction, involved in the baseline qualitative data collection (chapter 2), read and comment on the draft paper.</td>
</tr>
<tr>
<td>Ms Susan Renwick</td>
<td>Involved in the baseline quantitative data collection (chapter 2), provided commissioner’s oversight on the service being provided to this vulnerable group. Read and comment on the final draft of the paper.</td>
</tr>
<tr>
<td>Dr Jamie Rylance</td>
<td>Primary PhD supervisor. Provided support at all stages including reading drafts ethics, protocols and this final paper. Provided overall senior support for this project.</td>
</tr>
<tr>
<td>Dr Hassan Burhan</td>
<td>Joint senior author with Dr Jamie Rylance, Dr Burhan was first name author on the published baseline data. He read and commented on the final draft of the paper.</td>
</tr>
</tbody>
</table>

**3.4 This Paper as Part of the Thesis**

This paper builds on the quantitative study from chapter 2, giving a description of the lived experience of the participants who took part. The aim was to explore the perspective that heroin users have of COPD, treatment and access to care. This chapter allowed me to complement my experience of quantitative skills by furthering my understanding of qualitative data collection and analysis. This chapter adds a depth of understanding to the numbers seen in Chapter 2, fitting into the broader theme understanding the complex nature of chronic respiratory disease in disadvantaged populations. With Chapter 2, this paper gives further insight into the health needs of this population in Liverpool in a manner that may be useful for commissioners and service providers, as discussed further in Chapter 7.
3.5 Title Page

COPD in Heroin Smokers: a Patient Perspective

Nightingale R\(^1\), Griffiths, P\(^2\), Mortimer K\(^1\), Walker PP\(^3\), Byrne T\(^4\), Marwood K\(^4\), Morrison-Griffiths S\(^5\), Renwick S\(^5\), Rylance J\(^*1,6\), Burhan H\(^*2\)

* Rylance J and Burhan H are joint last name authors

No conflict of interest declared by authors.

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2 Royal Liverpool and Broadgreen University Hospitals, Liverpool, UK

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5 Liverpool Clinical Commissioning Group, Liverpool, UK

6 Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Blantyre, Malawi.

Author contributions

Design: RN, PG, KM, TB, SMG, SR, JR, PW, HB
Acquisition of data: RN, PG, KM, TB, SMG, HB
Analysis of data: RN, PG, JR
Interpretation of data: RN, PG, PW, JR, HB
Writing the manuscript, approval of the version to be published and agreement to be accountable for all aspects of the work: All authors

Funding

This project was funding by the medical research council doctoral training programme. (MRC DTP). Liverpool Clinical Commissioning Group funded the baseline data collection and a Health Foundation charity grant assisted with administrative support for the interviews.
3.6 Abstract

**Background:** Smoking rather than injecting heroin has become more common over the last twenty years. Although there is an increasing body of evidence describing high levels of COPD in heroin smokers, there is limited evidence documenting the impact this has on this population group.

**Aim:** We aimed to describe the experiences of heroin smokers with COPD in Liverpool, UK

**Design and Setting:** Participants were purposefully sampled for this qualitative study. Participants included were adults enrolled in an opioid replacement clinic run by Addaction in Liverpool, UK and whom had already engaged with spirometry testing for COPD as part of a previous study.

**Methods:** We performed semi-structured interviews with participants with spirometrically-confirmed COPD in opioid replacement clinics in Liverpool, UK. Data were analysed using a framework analysis approach.

**Results:** We invited 16 potential participants of whom 10 agreed to take part and were interviewed. Three themes common to all interviews were identified: functional measures of lung health that impacted on their activities of daily living, inhaler and medication perceptions with erratic use that was not concordant with their prescription, and the impact of difficulties accessing care.

**Conclusion:** These findings, along with previous studies highlighting the prevalence of COPD in this population, warrant efforts to integrate community COPD and opioid replacement services to improve outcomes for this vulnerable population.

**How this fits in:** There is a growing body of evidence of high levels of COPD in the heroin smoking population. This appears to happen at an earlier age than the general population. This qualitative study investigates the experiences of these patients and provides clinicians a new insight into the challenges facing this population. These results can be used to help guide the planning of future primary care service for this group of patients.
3.7 Introduction

Over the last two decades, heroin users have increasingly smoked rather than injected the drug, understanding this to be a method of harm reduction [1, 2]. This has, however, led many heroin smokers to develop chronic obstructive pulmonary disease (COPD) at an earlier age than typically seen in exclusive tobacco smokers [3, 4]. A recent study in Liverpool, UK, demonstrated that approximately 50% of heroin smokers have COPD or its overlap syndrome with asthma [3]. Those with COPD reported extensive respiratory symptoms - shortness of breath, cough and wheeze [5-7] - which are likely to lead to increased hospital admissions [8-10]. Screening heroin users for COPD may be an important part of providing care early in the course of the disease and limiting the burden of acute hospital care [4, 11].

There is limited evidence regarding patient experience among heroin users. We therefore sought insight into the experience and challenges faced by heroin smokers with COPD in order to shape future screening and treatment services. This qualitative study examines the lived experience of those with symptoms and a diagnosis of chronic lung disease, and of their experience of interfacing with healthcare services to access treatment.
3.8 Methods

We conducted semi-structured interviews with heroin smokers diagnosed with COPD as part of a screening programme between December 2017 and April 2018.

Study context

The interviews were carried out in Addaction community opioid replacement clinics as part of a COPD screening programme. Addaction is a large independent charity commissioned by the local city council public health department. The screening programme has been previously reported[3, 12]. Between December 2015 and June 2016, participants had been evaluated using respiratory-symptom-specific questionnaires, and spirometry to test their lung function. Follow-up screening took place between December 2017 and April 2018[3, 12].

Recruitment

Within Addaction clinics for opioid replacement therapy, we asked key workers to identify potential participants for the qualitative study. All had been diagnosed with COPD during baseline screening and were current or previous smokers of heroin. Potential participants were given study information prior to their appointment, and if they agreed to being interviewed, a key worker who knew them notified the study team. The key worker was not present during the interviews, but was available for support as necessary. Written informed consent was obtained from all participants.

Data collection

Interviews were led by a researcher (PG) independent of the quantitative screening study with experience of qualitative research and extensive medical knowledge of COPD. The researcher was aware the participant had COPD but knew no further clinical details. The interviews took place within the two large Addaction clinic sites in Liverpool, in rooms separate from the clinics to remove the participants from the clinical environment, and with refreshments provided. The researcher followed the topic guide which included: reported symptoms or problems, understanding of COPD, understanding of medications and experience of access to care. Open questions were asked with pre prepared probing questions to gain further information (Supplement one).
All interviews were digitally recorded and identified by participant number only.

**Analysis**

We used a framework analysis approach, taking five steps to results: familiarisation, coding, developing and applying a framework, charting and interpretation [13]. Each interview was transcribed verbatim, and the transcripts were read through by two researchers (RN and PG) for familiarisation. Following this, RN and PG agreed on the major coded themes based on the topic guide. The data were coded separately in Microsoft Excel, with the transcripts coloured coded for each theme in Microsoft Word. These codes were then shared with the wider research team (RN, PG, JR, HB) and a thematic framework was developed through discussion until a consensus was reached on the mapping of the codes. The themes were shared with Addaction staff members who were part of the research team to ensure they were accurate to the setting and true to the original topic guides (TB and KM).

**Ethics**

Ethical approval was gained from Health Research Authority (HRA) via the integrated Research Application System (IRAS) number: 235151.
3.9 Results

We invited 16 potential participants of whom 10 agreed to take part and were interviewed. The age range of those interview was 47-59 years, with eight males and two females taking part, all were Caucasian. The participants had a range of COPD severity measure by the GOLD classifications (mild n=4, moderate n=3, severe n=3)[14]. All were taking opioid replacement therapy with seven reporting they still smoke heroin. Following the interview framework, three themes common to all interviews were identified: functional measures of lung health that impacted on their activities of daily living, inhaler and medication perceptions with erratic use that was not concordant with their prescription, and the impact of difficulties accessing care.

Functional measures of lung health

All participants described their COPD in relation to the degree of functional limitation imposed by their symptoms. None of the participants described their COPD or lung disease in terms of medical outcomes such as spirometry results or breathlessness scores. Every participant had concerns about how COPD was affecting their everyday activities of daily life:

“You know every day I get up in the morning, I go to make a cup of coffee and I come back in and sit down and I’m gasping for breath and I can’t catch my breath, I just can’t get it, you know what I mean?” (Interview 5)

“I mean I often don’t go out, I struggle carrying shopping, I use one of them now, a bag over your shoulder, with the string, they help me to walk, a lot better. One time, I was putting the bags down, walk a bit, get my breath, again and again, oh God it was horrendous.” (Interview 10)

Participants described how their functional capacity had deteriorated over time. Eight participants recognised a worsening over a period of months or years. COPD was not explicitly mentioned in these cases, rather the participants described problems with their “lungs” or “chest” but did not necessarily attribute their problems to or label their condition as COPD:
“I was just speedy me. I was just one of them people, but now, now I just can’t even, even when my son was 7, I mean he’s 15 now, I was still doing the garden but I couldn’t breathe. I’ve stopped trying to do the garden I mean coz that nearly killed me, I mean it, bad palpitations, I think it would have killed me that day, my neighbour came out and said ‘go in, get in now!’ and stayed with me and everything.” (Interview 9)

“I can’t any more, I was quite a active say 10 years ago, but now I can’t run, can go slow on a bike but that’s it, couldn’t run if I wanted to...yeah, just from walking, or as I’ve said just getting out of bed, I can walk to the landing to look out the window and be standing panting, thinking ‘where’s the inhalers’ and it’s only when I have the inhalers that it seems to calm me down a bit.” (Interview 3)

Two participants did not perceive their chest to be a significant problem; both described functional limitation, but reported it as normal for them:

“I did run for the bus the other day and feel a bit out of breath, but most people would wouldn’t they? Running for the bus and exerting themselves, you know, at 8 o’clock in the morning.... I’ve got to be very fit and active every single day... So my chest isn’t too bad considering what I’ve put into it over the years, at least from my perspective it’s not.” (Interview 2)

“No....no it doesn’t stop me, and the inhalers I don’t use them every day, only when I need to, only when I’m coughing and short of breath I’ll use them then.....yeah but only when I’m coughing, sometimes I cough and I’m nearly puking... maybe 2 or 3 times a week.” (Interview 4)

**Inhalers and Medication perceptions**

All participants reported taking at least one inhaler and talked about them consistently during the interviews. Of the ten participants interviewed, seven reported that they had recently borrowed other people’s inhalers or medication to help their chest. The reasons for this were not always identifiable, but access to medication was a frequent difficulty:

“Well the last one I needed I got off me cousin coz she had a spare” (Interview 4)

“My girlfriend has one of those nebuliser things so I just throw myself on that, and erm, that kind of makes me feel ok.” (Interview 6)
“If there’s antibiotics in the house then I’ll use them instead [of going to a Doctor]… it’s like, I’ve been around drugs most of my life, so I’m not afraid to try an antibiotic or something if I think it might help me… well the wife has got asthma there, so err she got inhalers, a brown one and a blue one, and I’ll use them every now and again…. They’ve told me COPD is different to asthma so instead of using the wife’s stuff, I might need something else, a different one for my condition might be better.” (Interview 7)

Participants also reported the use of metered dose inhalers (MDI) as drug pipes, either by themselves or others:

“We used to make bongs out them, the blue one [salbutamol MDI], years ago, but God I couldn’t even look at doing that now it knocks me sick.” (Interview 9)

“You just [describes process of converting inhaler into a drug pipe]… Yeah yeah the blue ones, the hollow tube, […] I’ve seen a lot of people use them like that, like ‘rock pipes’ we called them… So it’s a common thing to do… It sounds mad that people are using things meant to help you breathe for that stuff doesn’t it?” (Interview 4)

There was generally poor knowledge and understanding surrounding inhalers, with participants confused between the name of the inhaler and the colour, for example describing a “blue inhaler” but pointing to a purple (Seretide) inhaler (Interview one). In general, participants described high usage of the “blue inhaler” (salbutamol) and inconsistent use of long acting medication such as tiotropium or formoterol. Participants reported that they used inhalers as and when they need them, and there appeared to be a lack of understanding of using longer term inhalers as prevention for some of the functional problems they described:

“I use the inhalers carefully, don’t waste them you know, use them as and when I feel I really need them, I don’t use them for the fun of it, I’ll only use them when I feel as though I’m struggling.” (Interview 8)

“Talking about the “blue and pink”? Nah I don’t use any of them regularly, only when I get bouts of it.” (Interview 4)

**Impact of access to care**

The difficulty in accessing both primary care appointments and hospital appointments was a recurring theme. The participants described travel to and from appointments as a barrier to attending both the GP surgery and the hospital. In some circumstances the cost of travel
was prohibitive and in others it was the practicalities of getting out of the house while being unwell. The participants suggested that they may attend more often if access to care was easier:

“well it’s 2 buses away, and it kills me to get there, but I love that doctor so I make the effort if I need to.” (Interview 1)

“It can be a bit of a task though, with the breathing and that, sometimes I only have to walk around the corner and I’m having a bad time... yeah well I have to walk here as well so that can be hard in itself, stop and rest about 20 times... you’d see me sat down on the road and all that, you know what I mean?” (Interview 6)

“I just can’t get there, even if I phone a taxi to come and take me, I just can’t get up and down the stairs.” (Interview 8)

The experience that participants had of their GPs and hospital doctors varied throughout the interviews, with participants describing their GP as “marvellous” (interview 1) and “I can’t fault him” (interview 10). All participants reported that seeing their own GP was difficult, either they saw a locum which they reported as a negative experience, or that getting an appointment via reception was difficult:

“well it’s hard to get an appointment at the doctors, to get my script, and God did I feel it when I ran out, really bad” (Interview 1)

“you know the credit on your phone to ring up, and you know when they say to ring at 8 o’clock in the morning, well try using somebody else’s phone, like I’ve had to use before, at 8 in the morning. That’s no good to me.” (Interview 10)

“maybe receptionists, when you phone up you’ve got to phone at certain times, waiting to get through to the receptionists, you see it’s like you wait for the phones to turn over at 8:20am and you might not get through ‘til 0920am and they’ve all gone, so, that’s not good....like I could have a problem like today, and I’ll go in or ring up and they’ll say ‘yeah we can fit you in in 2 weeks’ time’, well hang on, you know?” (Interview 8)

The participants generally reported that they did not attend hospital appointments. There were a variety of reasons for this including the feeling of stigma or that because chest
problems were self-inflicted. Several participants avoided secondary care environments due to negative associations with for example, a dying relative, or a negative experience with the hospital staff:

“I think they’re rushed off their feet, so you know, I think there’s sicker people than me to be seen to.... coz mine are self-inflicted, like they see sick children and it just shows you that I’ve done this to myself, you know?... because it’s self-inflicted isn’t it? I just feel embarrassed wasting the national health money...” (Interview 1)

“well they can’t do nothing can they, the doctors can’t do nothing for my chest the way it is, I have inhalers, I asked them about nebulisers, they said I don’t need a nebuliser, so, but I think I do like...I don’t know, I feel like they just look at you and think ‘ah its self-inflicted’ and that...” (Interview 5)

[when admitted with chest problem] “I’m on certain medication that they just won’t give you, like the methadone, they just won’t give you that, so I’ve got to lie there, like if I go in on a Friday I’ve got to lie there until Monday, with no nothin’. So you’re in bits by Monday, they sort your dose out, I know people might try and cheat the system, but you know, it goes on, I’m not going to abuse it and as doctors and nurses you’ve got to think ‘is this man on this?’  For one time in the hospital I was on 360ml a day, so when the doctors read that they thought ‘F*ck off no way’, you’d say as well. I mean I’m not on that now. They say to you get a stat dose of 20ml, but what that’s gonna do for me when I’m on 360? It doesn’t help. It’s experiences like that, the last thing I’d want to do is ring an ambulance if I can help it.” (Interview 8)
3.10 Discussion

Summary

Using qualitative interviews we have shown the key challenges to this cohort are lung health symptoms that impacted on their activities of daily living, inhaler and medication perceptions with erratic use that was not concordant with their prescription, and the impacts of difficulties accessing care. These themes occurred throughout the interviews and could help inform and develop respiratory services in this group of patients.

Comparison with exciting literature

The participants’ main focus was the functional limitation that they experienced in their activities of daily living as a result of their COPD. No participant discussed the details of their medical diagnosis, the staging of their COPD or used medical scoring such as MRC and CAT to describe their COPD. To the best of our knowledge there are no studies that specifically describe the impact and functional limitations of COPD in heroin smokers, however the themes identified in this study are similar to studies of tobacco smokers. In a large pan-European study examining COPD patients and their experience of acute exacerbations, there was wide variability in reported symptoms between patients (reported at 62.7%), high levels of self-medication, and poor understanding of their condition [14]. The impact of COPD-related symptoms on activities of daily living has been evaluated previously, with there being a high prevalence of impaired functioning amongst COPD patients across a wide range of domains. The impairment does not clearly correlate with standard clinical measures such as degree of airflow obstruction or level of dyspnoea [15, 16]. Furthermore, functional limitation was common amongst the participants in our study and was often deemed to be ‘normal’ by individuals. Relying on objective measures of COPD severity in this patient population may not identify individuals who would benefit from more targeted interventions, such as pulmonary rehabilitation, aiming to improve symptoms and level of functioning with regards to activities of daily living.

In general, our participants appeared to be taking COPD medication in an irregular and often self-directed manner. In some, inhalers were used as a vehicle for smoking drugs rather than for their intended purpose. The engagement with the primary care system in the UK was mixed, with some participants having an excellent experience of their GP, whist
others found significant barriers to attending primary care with travel and access to the GP being the principle negative factors. Participants universally found accessing hospital treatment difficult, with stigma and a feeling of having a “self-inflicted” illness limiting attendance at the hospital.

Poor adherence and a lack of knowledge or trust in medication has been reported in other studies of COPD patients with overuse, underuse and alteration from medication schedule commonplace [17]. In a cross-sectional study of 173 patients with COPD attending outpatient clinics, 29.5% of attendees had “low adherence” to medication [18]. The theme of accessing prescription medication from peers or family members is also not unique to our population, with one study in students finding that those who access medication from peers were also more likely to use illicit drugs [19]. Stigma and significant barriers to accessing both primary and secondary are common across illicit drug users, with reports of “dissonant care” commonplace with other qualitative and narrative studies in this population describing similar findings to the analysis of our interviews [20-23].

**Strengths and limitations**

The main limitation of this study is the small number of interviews conducted and the breadth of the interviews conducted. It may have added to the depth of knowledge if healthcare providers had also been interviewed, and further study in this area would be informative. The participants who declined to take part may have led to bias, with those happier to engage or those with strong opinions about their COPD potentially more likely to take part. This study has however offered a new and unique view on the possible barriers facing heroin smokers with COPD.

**Implications for research and practice**

Our data highlight important considerations in the development of COPD services for drugs users. Clinicians should consider functional outcomes as well as clinical outcomes and objective scoring systems when discussing COPD treatment with the patient. There is potential that functional goals would be welcomed by this patient group and may help motivate the attendance to care and adherence to treatment. The use of self-medicated inhalers, nebulisers and other drugs makes clinical assessment even more challenging in this population; it is highly likely that the standard methods of assessing “medication pick up” at
pharmacies does not provide an accurate picture, and that self-reported usage may be key
to determining the real clinical need. Alongside this the overuse of some inhalers,
potentially as drug paraphernalia, adds to an already complex clinical picture. The access to
respiratory care for this patient group is limited, with barriers including transport to
hospitals and a feeling of stigma. There is potential that providing respiratory care centred
around venues where patients attend opioid replacement therapy would improve
continuity of care and assist in obtaining accurate medication histories. This research
highlights the complex needs of heroin smokers with COPD and the need to consider their
functional limitations, medication management and access to care in future planning of
respiratory services.

3.11 References

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Chapter 4: Non-Communicable Respiratory Disease and Air Pollution Exposure in Malawi: a Cross-Sectional Study

4.1 Chapter Layout

This chapter is presented as a copy of the Word document that was accepted for publication. For ease of reading I have included the tables and figures in the text and labelled them to flow with the whole thesis (at submission the table and figures were presented as a separate document). I have labelled each section 4.’X’ for indexing. The PDF of the paper can be found in appendix chapter 4 section 1. The ‘online supplement’ can be found in the Appendix for Chapter 4 Section 2.

4.2 My Contribution to the Paper

The data for this paper is derived from the BOLD (Burden of Obstructive Lung Disease) Survey in Malawi. During multiple visits to Malawi I worked with the field team and Dr Sarah Rylance to obtain and clean the primary data. I worked with the MLW technical team, Mr Graham Flitz, Dr Maia Lesosky and Prof. Kevin Mortimer to obtain and organise the air pollution data. I did all the initial data cleaning (after initial review of spirometry traces by the BOLD co-ordinating centre), merging, analysis and interpretation. I wrote the original draft of the paper and edited the subsequent revisions based on feedback from co-authors. I completed the submission process for the paper, although for logistical reasons Prof. Kevin Mortimer was corresponding author. After feedback from reviewers and due to my maternity leave, Dr Lesosky did further analysis and produced Figure 3 of this paper with remote input from myself and she also edited Table 3-6. The final textual revisions were jointly done by myself, Prof. Mortimer and Dr Lesosky. I was back from maternity leave after preliminary acceptance of the manuscript for publication, and I co-ordinated the replies to the editors, and scrutinised and corrected the final proofs.
4.3 Contribution of Other Authors to the Paper

<table>
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<tr>
<th>Name</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Maia Lesosky</td>
<td>Provided statistical support, in particular provided assistance with the air pollution data, provided methodology and statistical edits on hearing back from the reviewers. Read and edited all version of this paper.</td>
</tr>
<tr>
<td>Dr Graham Flitz</td>
<td>Was involved in carrying out the air pollution data collection</td>
</tr>
<tr>
<td>Dr Sarah Rylance</td>
<td>Worked with and co-ordinated the field team in Chikwawa (Malawi), read and edited the first draft of paper.</td>
</tr>
<tr>
<td>Dr Jamilah Meghji</td>
<td>Carried out the urban BOLD study and assisted with set up of the sampling frame for rural BOLD. Read and comment on the first draft of this paper</td>
</tr>
<tr>
<td>Prof. Peter Burney</td>
<td>The head of the BOLD centre. Read and commented on the draft.</td>
</tr>
<tr>
<td>Dr John Balmes</td>
<td>Supervised Mr Graham Flitz in collected the air pollution data and setting up the study, provided air pollution data advice and read and commented on all version of this paper.</td>
</tr>
<tr>
<td>Prof. Kevin Mortimer</td>
<td>Provided PhD supervision, was the senior authors on the CAPS paper, set up and designed the study with BOLD centre in Chikwawa. Read and edited all version of this paper.</td>
</tr>
</tbody>
</table>

4.4 This Paper as Part of the Thesis

In a move from the disadvantaged populations at high-risk of respiratory disease in Liverpool, this paper is based in rural Malawi. It focused on another disadvantaged population: a rural community who have extremely high exposure to air pollution from burning biomass for cooking, heating and lighting. In this paper I take the opportunity to evaluate a cohort of individuals who received a cleaner-burning biomass-fueled cookstove during an intervention study (CAPS). This enables some assessment of the possible impact of the cleaner cooking methods, looks more widely at the prevalence of abnormal spirometry in this community, and describes possible risk factors associated with it. Like Chapter 2, it is a quantitative study which uses spirometry as the main outcome measure.
4.5 Title Pages

Non-Communicable Respiratory Disease and Air Pollution Exposure in Malawi: a Cross-Sectional Study

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Acquisition of data: RN, KM, PB, JB

Analysis of data: RN, ML, GF, SR

Interpretation of data: RN, ML, GF, SR, JM, PB, JB, KM

Writing the manuscript, approval of the version to be published and agreement to be accountable for all aspects of the work: All authors
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**Running Head**
NCD-Respiratory in Malawi.

**Associated Funding**
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**Acknowledgements**
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**Impact**
The characteristics of non-communicable respiratory diseases in sub-Saharan Africa may be different to previously thought with more spirometric restriction and less obstruction including household air pollution-associated COPD. There is a need for clinically- and cost-effective approaches for the prevention and control of non-communicable respiratory diseases in sub-Saharan Africa.
At a Glance:

**Scientific Knowledge**

Non-communicable respiratory diseases and exposure to air pollution are thought to be important causes of morbidity and mortality in sub-Saharan African adults. Recent Burden of Obstructive Lung Disease (BOLD) studies found a high burden of spirometric restriction but little spirometric obstruction in several sub-Saharan African countries and no association between spirometric obstruction and use of dirty-burning fuels. It is not known whether an association between spirometric obstruction and solid fuel use would be seen if personal exposure to air pollution were measured in addition to self-reported exposure. The Cooking And Pneumonia Study (CAPS) – a trial of cleaner burning biomass-fueled cookstoves on pneumonia in children under the age of five in rural Malawi – offered the opportunity to explore this and other secondary trial outcomes in adults.

**What this study adds:**

In adults living in Chikhwawa, rural Malawi: 13.6% of participants had chronic respiratory symptoms (mainly cough); over 40% had abnormal spirometry (mainly spirometric restriction); day-to-day air pollution exposures were approximately three times the World Health Organization upper safety limit; air pollution exposures were not associated with demographic, clinical or spirometric characteristics; and there was no association between CAPS trial arm and any of the secondary trial outcomes.
4.6 Abstract

**Rationale:** Non-communicable respiratory diseases and exposure to air pollution are thought to be important contributors to morbidity and mortality in sub-Saharan African adults.

**Objectives:** We set out to explore the prevalence and determinants of noncommunicable respiratory disease among adults living in Chikhwawa District, Malawi.

**Methods:** We performed a cross-sectional study among adults in communities participating in a randomised controlled trial of a cleaner-burning biomass-fuelled cookstove intervention (CAPS) in rural Malawi. We assessed chronic respiratory symptoms, spirometric abnormalities, personal exposure to air pollution (fine particulate matter < 2.5 μm in aerodynamic diameter [P.M2.5] and carbon monoxide (CO)). Prevalence estimates were calculated; multivariable and intention-to-treat analyses were done.

**Results:** One thousand four hundred eighty-one participants (mean (SD)) age 43·8 (17·8), 57% female) were recruited. The prevalence of chronic respiratory symptoms, spirometric obstruction and restriction were 13·6% (95% CI:11.9-15.4), 8·7% (95% CI:7·0-10·7) and 34·8% (95% CI:31·7-38·0), respectively. Median 48-hour personal PM$_{2.5}$ and CO exposures were 71·0 μg/m$^3$ (IQR:44·6-119·2) and 1·23 ppm (IQR:0·79-1·93), respectively. Chronic respiratory symptoms were associated with current/ex-smoking (OR=1·59 (95% CI:1·05-2·39)), previous TB (OR=2·50 (95% CI:1·04-15·58)) and CO exposure (OR=1·46 (95% CI:1·04-2·05)). Exposure to PM$_{2.5}$ was not associated with any demographic, clinical or spirometric characteristics. There was no effect of the CAPS intervention on any of the secondary trial outcomes.

**Conclusion:** The burden of chronic respiratory symptoms, abnormal spirometry and air pollution exposures in adults in rural Malawi is of considerable potential public health importance. We found little evidence that air pollution exposures were associated with chronic respiratory symptoms or spirometric abnormalities and no evidence that the CAPS intervention had effects on the secondary trial outcomes. More effective prevention and
control strategies for non-communicable respiratory disease in sub-Saharan Africa are needed.
4.7 Introduction

Highly polluting fuels, including animal dung, crop residues, wood, charcoal and kerosene, are used by almost half the world’s population to provide energy for cooking, heating and lighting [1-3]. These fuels are typically burned in and around the home environment in inefficient ways – e.g. open fires – which leads to high levels of air pollution in and immediately outside of homes. The World Health Organization (WHO) has estimated that exposure to household air pollution leads to over four million deaths each year [3]. The latest Global Burden of Disease Study estimates this number is closer to 2·5 million but even these lower estimates represent a substantial burden of morbidity and mortality that falls particularly heavily on the world’s poor [4]. Household air pollution has been considered to increase the risk of pneumonia in children and of chronic obstructive pulmonary disease (COPD) and cardiovascular disease in adults [1-3].

In 2017, we published the findings of a cluster-randomised controlled trial of introducing a cleaner-burning biomass-fuelled cookstove to prevent pneumonia in children under 5 years of age in rural Malawi (the Cooking and Pneumonia Study – CAPS) [5]. CAPS is one of a small number of trials done to date to evaluate the effects of reducing biomass smoke exposure on health outcomes and is the largest trial of a cookstove intervention on health outcomes conducted anywhere in the world (n=10 750 children from 8 626 households across 150 clusters). The major finding of this trial was that there was no difference between the intervention and control groups among children in pneumonia incidence defined using the criteria of the Integrated Management of Childhood Illness (IMCI) programme. This unexpected finding has cast some doubt on the assumptions made by the Global Alliance for Clean Cookstoves (GACC) that cleaner cookstoves and fuels save lives [6-11].

Herein we report the findings of a cross-sectional study of the prevalence and determinants of non-communicable respiratory disease among adults living in communities that participated in CAPS which addresses the pre-specified secondary trial objective of determining prevalence and determinants of obstructive lung disease in adults in rural Malawi [5]. In this setting, use of highly polluting fuels for day-to-day household energy
requirements is the norm and therefore a high burden of COPD associated with household air pollution was expected.

4.8 Methods

Study design
We did a cross-sectional study of the prevalence and determinants of non-communicable respiratory disease among adults living in Chikhwawa District, Malawi.

Setting
Chikhwawa is approximately 50 kilometres from the nearest city, Blantyre, on the southern Shire River Valley, and consists primarily of subsistence farmers living in rural village communities. The Malawi College of Medicine Research Ethics Committee (ethics committee reference number P.11/12/1308) and the Liverpool School of Tropical Medicine Research Ethics Committee (ethics committee reference number 12.40) approved the CAPS trial protocol that includes this work, a summary of which was published by The Lancet [12]. Study registration: ISRCTN 59448623.

Participants
Following community engagement events that included village leaders and other community representatives, a list of all the adults living in each of the 50 villages participating in CAPS in Chikhwawa was obtained from local community health workers known as Health Surveillance Assistants. These lists were collated and used by an independent statistician at the BOLD (Burden of Obstructive Lung Disease) centre in London to obtain a population-representative sample of adults over the age of 18 with stratification by age and sex. All potential participants sampled in this way were then individually invited to participate with written informed consent (or witnesses thumbprint for those unable to read and write) obtained from those who agreed. People who were acutely unwell, not permanent residents or pregnant were excluded.

Procedures
Fieldworkers who had undergone study-specific training and met the required quality standards did home visits according to standardised operating procedures. With the
exception of the air pollution monitoring procedures which are not part of the BOLD study protocol, all procedures were conducted in accordance with the BOLD study protocol which has been described previously [14]. Minimal demographic information was collected from participants who declined to participate in the full study. Fieldworkers administered BOLD study questionnaires in the local language, Chichewa. Height and weight were measured using a portable stadiometer and scales. All eligible participants were asked to do pre- and post-bronchodilator spirometry which BOLD centre certified fieldworkers performed to European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines using the ndd EasyOne Spirometer (ndd Medical Technologies; Zurich, Switzerland)[14]. Up to three repeat visits were arranged to achieve the required spirometry quality standards. Spirometry data were sent electronically to the BOLD centre for quality control.

Personal exposures to particulate matter <2.5 μm in aerodynamic diameter (PM$_{2.5}$) and carbon monoxide (CO) were measured continuously for 48 hours using the indoor air pollution (IAP) 5000 Series Monitor (Aprovecho Research Center). The IAP 5000 sampled air from the breathing zone using a short tube and logged continuous PM$_{2.5}$ and CO using a light-scattering photometer and an electrochemical cell CO sensor, respectively. All monitors were calibrated at the Aprovecho Research Center prior to use in the study. Monitors were worn in small backpacks apart from during sleep when they were kept beside the sleeping mat or bed.

**Variables**

Clinical outcomes were presence or absence of specific symptoms as assessed by questionnaire. The questions (outcomes) asked were as follows: Do you usually have a cough when you don’t have a cold (cough outcome)? Do you usually bring up phlegm from your chest (phlegm outcome)? Have you had wheezing/whistling in your chest at any point in the last 12 months, in the absence of a cold (wheeze outcome)? Do you have shortness of breath when hurrying on the level or walking up a slight hill (dyspnoea outcome)? And have your breathing problems interfered with your daily activities (functional limitation outcome)? A composite variable for any symptoms was created by defining as positive if an individual reported any of the above symptoms (any symptoms outcome).
Continuous FEV$_1$ and FVC spirometry values were used in the primary analysis. Spirometric obstruction and restriction were defined according to the NHANES III Caucasian reference range lower limits of normal[15].

Exposures of interest included personal exposure to PM$_{2.5}$ or CO as measured by the personal monitoring device, and two exposures assessed by questionnaire: smoking status and previous episode of TB. A questionnaire assessed variable asking for any biomass exposure was considered, but as the majority (>99%) indicated yes, it was not included in any modelling.

Raw PM$_{2.5}$ and CO exposures were corrected for background levels using calibration values for each monitoring period. In cases where calibration data were missing or corrupted (<5%), aggregated mean calibration values were used. Observations where less than 2000 min of time were recorded were excluded, as were monitoring periods affected by device malfunction. Both PM$_{2.5}$ and CO were log$_{10}$ transformed for presentation and inclusion in models due to large positive skew.

Potential confounders/effect modifiers included were Body Mass Index (BMI), and/or height (cm) and weight (kg) variables, as well as age, years of education, and sex.

**Study size**
We initially invited 2000 people to participate but increased this to 3000 to achieve the required sample size. Participants were stratified into two age groups: 18-39 years and 40 years or above. We estimated that, after allowing for unequal age and gender distributions, refusals and inability to provide spirometry measurements of acceptable quality, a sample of just 300 participants in any one gender / age stratum (1200 total) would provide an estimate of chronic airflow limitation prevalence in this stratum with a precision (95% CI) of ±3.3 to ±5.0% assuming a prevalence of 10 to 25%.

**Statistical methods**
Univariate analysis was completed using descriptive statistics to explore the characteristics of the study population. Descriptive analysis is presented for clarity using categorical
versions of BMI (underweight, normal, overweight or obese) and categorical versions of age, however age, weight and height were entered into models as continuous variables. Participants who completed the study in full or in part were assessed for selection bias using the chi-square and Student’s t-test. Multivariable logistic regression was used to estimate the strength of the association between measured exposure variables and dichotomous clinical outcomes, adjusting for potential confounders. All models were adjusted for age, sex, weight, and height. Linear multivariable regression was used to estimate the association between exposures and continuous lung function values (FEV₁, FVC, FEV₁/FVC). Secondary exploratory trial efficacy analyses were by intention-to-treat (ITT). Statistical significance was nominally set at alpha = 0.05. Stata version 14.2 and R version 3.4 statistical software was used for data analysis (Stata Statistical Software: R.14; StataCorp LLC, College Station, TX).

Role of the funding source
The funders had no role in the study design, data collection, analysis, interpretation or writing of the report. The corresponding author had full access to all the study data and had final responsibility for the decision to submit for publication.

4.9 Results
Between August 2014 and July 2015, we attempted to contact the 3000 adults sampled to invite them to participate of whom 1481 (49.4%) consented and completed BOLD study questionnaires. Of these, 950 (64.6%) went on to do spirometry; the remaining 520 (35.3%) were unable to do spirometry because they could not physically co-operate with the procedure (n=258; 48.9%), had a fieldworker-determined contra-indication (n=193; 37%) or refused (n=69; 13.3%). Of the 1481 participants, 1144 (77.2%) underwent personal air pollution exposure monitoring. There were 424 (28.6%) participants from CAPS intervention or control households (Figure 1).
The mean age (SD) of participants was 43·8 (17·8) years and 57% were female (Table 1). Just over half the participants had been educated only to primary school level with a third having had no formal school education. The use of biomass fuels for cooking was almost universal (99·8%).
### Table 1: Demographic and clinical characteristics (n=1481)

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<th>Characteristic</th>
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<td>40-49</td>
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<td>60-69</td>
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<td>&gt;70</td>
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<td><strong>Sex</strong></td>
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<tr>
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<td>Up to 10 pack years</td>
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<tr>
<td><strong>BMI group, kg/m²</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight (BMI&lt;18·5)</td>
<td>188 (14·4)</td>
<td></td>
</tr>
<tr>
<td>Normal (BMI 18·5-25)</td>
<td>945 (72·5)</td>
<td></td>
</tr>
<tr>
<td>Overweight (BMI 25 -30)</td>
<td>130 (10·0)</td>
<td></td>
</tr>
<tr>
<td>Obese (BMI &gt;30)</td>
<td>40 (3·1)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>178 (12·0)</td>
<td></td>
</tr>
<tr>
<td><strong>Previous TB</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1434 (92·3)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>47 (3·2)</td>
<td></td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>165 (11·1)</td>
<td></td>
</tr>
<tr>
<td>(do you usually cough when you don’t have a cold?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum</td>
<td>38 (2·6)</td>
<td></td>
</tr>
<tr>
<td>(Do you usually bring up phlegm from your chest)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheeze</td>
<td>23 (1·6)</td>
<td></td>
</tr>
<tr>
<td>(Have you had wheezing/whistling in your chest at any point in past 12m in the absence of a cold)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRC dyspnoea II (do you have shortness of breath when hurrying on the level or walking up a slight hill?)</td>
<td>23 (1·6)</td>
<td></td>
</tr>
<tr>
<td>Any respiratory Symptoms. (Any of cough, sputum, wheeze without cold, exertional breathlessness as above)</td>
<td>201 (13·6)</td>
<td></td>
</tr>
<tr>
<td>Functional limitation (have breathing problems interfered with your usual daily activities)</td>
<td>43 (2·9)</td>
<td></td>
</tr>
</tbody>
</table>

One or more chronic respiratory symptom was reported by 201 (13·6% (95% CI 11·9 - 15·4)) participants (Table 1 and Figure 2). Respiratory symptoms were more commonly reported with increasing age. Regular cough was reported by 11·1% (95% CI 9·6 - 12·8) while 2·6%...
(95% CI 1·9 - 3·5) reported usually coughing up phlegm. Breathlessness and wheeze were less commonly reported: 1·6% (95% CI 1·0 - 2·3) and 1·6% (95% CI 1·0 - 2·3), respectively. Respiratory symptoms that limited functional ability were reported by 2·9% (95% CI 2·2 - 3·9). A previous diagnosis of TB was reported by 3·2% (95% CI 2·4 - 4·2) which was more common with increasing age. Current or former smoking was reported by 22·1% (95% CI 20·1 - 24·3) although only 4·3% had greater than a 10 pack-year history. Many participants (14·4%) had a low BMI.

Figure 2: Age stratified prevalence of respiratory symptoms

Of the 950 participants who did spirometry, 886 (93·2%) achieved BOLD study quality standards and were included in the analyses. Factors associated with declining or not completing spirometry to ERS/ATS standards were: older mean age [48 vs. 39 years (p<0·001)]; being female [65% vs. 51% (p<0·001)]; lower mean years of education [2 vs. 5 years (p<0·001)]; lower mean BMI [20·7 vs. 21·3 (p<0·001)]. As shown in Table E1 in the Online Data Supplement, participants who completed spirometry were less likely to have cough, wheeze and dyspnoea compared to those who didn’t complete spirometry and were slightly more likely to have phlegm and functional limitation although none of these differences were statistically significant. Spirometric obstruction and restriction were present in 8·7% (95% CI: 7·0 - 10·7) and 34·8% (95% CI: 31·7 - 38·0) of the 886 participants that met the required quality standards, respectively.
Of the 1144 participants (mean age (SD) 43.9 (17.9) years; 57% female) who underwent personal exposure monitoring, 1117 (97.6%) had valid exposure monitoring records. The 48-hour median personal PM$_{2.5}$ and CO exposures were 71.0 μg/m$^3$ (IQR: 44.6 - 119.2) and 1.23 ppm (IQR: 0.79 - 1.93), respectively. There was weak correlation between these two air pollution exposure measures (Figure 3).

**Figure 3: Scatter plot between personal exposure to PM$_{2.5}$ and CO**

In logistic multivariable analysis, smoking (OR=1.56 (95% CI: 1.01 - 2.41)) and previous TB (OR=2.81 (95% CI: 1.19 - 6.08) were associated with cough (Table 2 and Table E1 in the Online Data Supplement). In continuous multivariable analysis, both FEV$_1$ and FVC had a negative association with increasing age and were higher for men compared to women (Table 3). Smoking (coefficient estimate = -0.09 (95% CI: -0.16 - -0.01) and previous TB (coefficient estimate = -0.46 (95% CI: -0.64 - -0.28)) were associated with FEV$_1$ and previous TB was associated with FVC (coefficient estimate = -0.35 (95% CI: -0.56 - -0.15)). There was no association between personal exposure to PM$_{2.5}$ and any of the demographic and clinical
characteristics or spirometric indices (Tables 4 and 5). The only statistically significant association was between exposure to CO and reporting “any chronic respiratory symptoms” (OR = 1·46 (95% CI: 1·04 - 2·05)). There were no statistically significant associations between personal exposure to CO and any other demographic and clinical characteristics or to any spirometric indices. There were 424 (227 intervention; 197 control) participants in the CAPS ITT population, however not all of them had complete spirometry (133 without) or exposure measures (87 without). There were no differences in respiratory symptoms, spirometric indices or exposure to CO or PM$_{2.5}$ between the intervention and control groups (Table 6).

Table 2: OR (95% CI) for chronic respiratory symptom outcomes estimated by multivariable logistic regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cough</th>
<th>Phlegm**</th>
<th>Wheeze**</th>
<th>Dyspnoea**</th>
<th>Functional limitation</th>
<th>Any symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1·01 (1·00, 1·02)</td>
<td>1·00 (0·97, 1·02)</td>
<td>1·02 (0·99, 1·05)</td>
<td>1·01 (0·98, 1·04)</td>
<td>1·00 (0·95, 1·02)</td>
<td>1·00 (0·97, 1·02)</td>
</tr>
<tr>
<td>Male</td>
<td>ref</td>
<td>Ref</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>Female</td>
<td>0·78 (0·49, 1·25)</td>
<td>1·02 (0·42, 2·51)</td>
<td>0·97 (0·30, 3·28)</td>
<td>3·08 (0·88, 11·65)</td>
<td>1·17 (0·28, 2·37)</td>
<td>1·08 (0·70, 1·67)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>1·56 (1·01, 2·41)</td>
<td>1·37 (0·58, 3·15)</td>
<td>0·77 (0·20, 2·47)</td>
<td>1·85 (0·51, 6·07)</td>
<td>0·65 (0·18, 1·93)</td>
<td>1·59 (1·05, 2·39)</td>
</tr>
<tr>
<td>Previous TB: No</td>
<td>ref</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>Yes</td>
<td>2·81 (1·19, 6·08)</td>
<td></td>
<td></td>
<td></td>
<td>2·64 (0·40, 9·95)</td>
<td>2·50 (1·04, 15·58)</td>
</tr>
<tr>
<td>Years education</td>
<td>0·97 (0·92, 1·02)</td>
<td>0·90 (0·81, 1·00)</td>
<td>0·99 (0·86, 1·13)</td>
<td>0·96 (0·83, 1·10)</td>
<td>1·06 (0·96, 1·16)</td>
<td>0·98 (0·93, 1·03)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: Ref = reference; TB = tuberculosis. All models were also adjusted for weight (kg) and height (cm); total n = 1,303 owing to missing weight data. *Only one person had both TB and wheeze, one person had both TB and phlegm, and one person had both TB and dyspnea; TB was excluded from these model
Table 3: Coefficient estimates (95% CI) for continuous spirometry outcomes FEV₁, FVC, FEV₁/FVC ratio (n=886)

<table>
<thead>
<tr>
<th>Variable</th>
<th>FEV₁</th>
<th>FVC</th>
<th>FEV₁/FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>-0.02 (-0.02, -0.02)</td>
<td>-0.01 (-0.01, -0.01)</td>
<td>-0.28 (-0.31, -0.24)</td>
</tr>
<tr>
<td>Male</td>
<td>Ref</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>Female</td>
<td>-0.53 (-0.60, -0.45)</td>
<td>-0.70 (-0.78, -0.62)</td>
<td>1.37 (0.18, 2.56)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>Ref</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>-0.09 (-0.16, -0.01)</td>
<td>-0.05 (-0.14, 0.04)</td>
<td>-1.76 (-2.99, -0.53)</td>
</tr>
<tr>
<td>Previous TB: No</td>
<td>Ref</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>Previous TB: Yes</td>
<td>-0.46 (-0.64, -0.28)</td>
<td>-0.36 (-0.56, -0.15)</td>
<td>-7.83 (-10.74, -4.91)</td>
</tr>
<tr>
<td>Years education</td>
<td>0 (0, 0.01)</td>
<td>0 (-0.01, 0.01)</td>
<td>0.18 (0.05, 0.3)</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: Ref = reference; TB = tuberculosis. All models were also adjusted for weight (kg) and height (cm).*

Table 4: OR (95% CI) for symptom outcomes estimated by multivariable logistic regression in participants with exposure measurements (n=985)

<table>
<thead>
<tr>
<th>Ever smoked (ref: never smoked)</th>
<th>Cough</th>
<th>Phlegm**</th>
<th>Wheeze**</th>
<th>Dyspnoea**</th>
<th>Functional limitation</th>
<th>Any symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smoked</td>
<td>1.72 (1.02, 2.91)</td>
<td>0.99 (0.37, 2.53)</td>
<td>0.35 (0.02, 2.32)</td>
<td>2.62 (0.56, 11.24)</td>
<td>0.78 (0.20, 2.47)</td>
<td>1.67 (1.02, 2.71)</td>
</tr>
<tr>
<td>Previous TB: No</td>
<td>2.87 (1.07, 6.87)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.47 (0.91, 6.07)</td>
</tr>
<tr>
<td>Previous TB: Yes</td>
<td>1.29 (0.93, 1.77)</td>
<td>1.50 (0.83, 2.54)</td>
<td>2.12 (0.96, 4.16)</td>
<td>1.27 (0.48, 2.88)</td>
<td>1.45 (0.81, 2.43)</td>
<td>1.46 (1.04, 2.05)</td>
</tr>
<tr>
<td>CO (log₁₀ ppm)</td>
<td>1.02 (0.95, 1.13)</td>
<td>0.96 (0.88, 1.11)</td>
<td>1.00 (0.87, 1.38)</td>
<td>1.11 (0.89, 1.67)</td>
<td>0.99 (0.90, 1.16)</td>
<td>1.02 (0.95, 1.11)</td>
</tr>
<tr>
<td>PM₂.₅ (log₁₀ µg/m³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Definition of abbreviations: CO = carbon monoxide; PM₂.₅ = particulate matter, 2.5 mm in aerodynamic diameter; ref = reference; TB = tuberculosis. All models were adjusted for weight (kg), height (cm), age (yr), sex (male, female), and years of formal education. *Only one person had both TB and wheeze, one person had both TB and phlegm, and one person had both TB and dyspnea; TB was excluded from these models.*
Table 5: Coefficient estimates (95% CI) for continuous spirometry outcomes FEV₁, FVC, FEV₁/FVC ratio in participants with personal air pollution exposure measurements (n=886)

<table>
<thead>
<tr>
<th>Variable</th>
<th>FEV₁</th>
<th>FVC</th>
<th>FEV₁/FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>-0.02 (-0.02, -0.01)</td>
<td>-0.01 (-0.02, -0.01)</td>
<td>-0.28 (-0.35, -0.20)</td>
</tr>
<tr>
<td>Male</td>
<td>Ref</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>Female</td>
<td>-0.58 (-0.61, -0.44)</td>
<td>-0.70 (-0.79, -0.60)</td>
<td>1.25 (-0.09, 2.56)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>Ref</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>-0.1 (-0.19, -0.02)</td>
<td>-0.07 (-0.16, 0.03)</td>
<td>-1.83 (-3.20, -0.45)</td>
</tr>
<tr>
<td>Previous TB: No</td>
<td>Ref</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>Previous TB: Yes</td>
<td>-0.32 (-0.52, -0.11)</td>
<td>-0.26 (-0.49, -0.02)</td>
<td>-6.16 (-9.48, -2.85)</td>
</tr>
<tr>
<td>Years education</td>
<td>0 (0, 0.01)</td>
<td>0 (-0.01, 0.01)</td>
<td>0.15 (0.01, 0.29)</td>
</tr>
<tr>
<td>CO (log₁₀ ppm)</td>
<td>0.01 (-0.04, 0.06)</td>
<td>0.01 (-0.04, 0.07)</td>
<td>0.13 (-0.68, 0.94)</td>
</tr>
<tr>
<td>PM₂.₅ (log₁₀ μg/m³)</td>
<td>0 (-0.02, 0.01)</td>
<td>0 (-0.01, 0.01)</td>
<td>-0.11 (-0.29, 0.08)</td>
</tr>
</tbody>
</table>

For definition of abbreviations, see Table 4. All models were also adjusted for weight (kg) and height (cm)

Table 6: CAPS ITT secondary trial analyses (n=424)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention (n=227)</th>
<th>Control (n=197)</th>
<th>Intervention vs. Control Coefficient Estimate (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms (n (%))</td>
<td>22 (9.7%)</td>
<td>26 (13.2%)</td>
<td>0.90 (0.45,1.82)**</td>
<td>0.87</td>
</tr>
<tr>
<td>FEV₁ [med (IQR)]</td>
<td>2.81 (2.39, 3.26)</td>
<td>2.77 (2.40, 3.10)</td>
<td>0.08 (-0.06, 0.22)</td>
<td>0.26</td>
</tr>
<tr>
<td>FVC [med (IQR)]</td>
<td>3.37 (2.88, 3.91)</td>
<td>3.31 (2.83, 3.86)</td>
<td>0.04 (-0.13, 0.21)</td>
<td>0.62</td>
</tr>
<tr>
<td>Mean CO [med (IQR)]</td>
<td>1.13 (0.79, 1.90)</td>
<td>1.28 (0.82, 1.79)</td>
<td>0.67 (-0.60, 1.96)</td>
<td>0.30</td>
</tr>
<tr>
<td>Mean PM₂.₅ [med (IQR)]</td>
<td>67.90 (44.72, 112.95)</td>
<td>64.47 (40.73, 101.80)</td>
<td>-931.6 (-2073.6, 209.7)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Definition of abbreviations: CAPS = Cooking and Pneumonia Study; CI = confidence interval; CO = carbon monoxide; IQR = interquartile range; PM₂.₅ = particulate matter, 2.5 mm in diameter. Mean exposure per individual is calculated, and the median (IQR) of those values is reported. *Odds ratio (95% CI).
4.10 Discussion

The main findings of this cross-sectional study of the burden and determinants of non-communicable respiratory disease in adults living in Chikhwawa, rural Malawi were that: 13·6% of participants had chronic respiratory symptoms (mainly cough); over 40% had abnormal spirometry (mainly spirometric restriction); day-to-day air pollution exposures were approximately three times the WHO upper safety limit; and there was no association between CAPS trial arm and any of the secondary trial outcomes in the subset of adults included both in this study and the trial.

The finding of a low prevalence of spirometric obstruction in this setting - where highly polluting fuels are almost universally used for household energy needs and where exposure to household air pollution is high – is surprising given that household air pollution-associated COPD has been suggested to be a major global health problem and as such would be expected to be highly prevalent in our study setting[16-19]. This finding is consistent with an emerging body of evidence challenging the dogma that exposure to household air pollution is a major cause of COPD including a recent pooled analysis of BOLD Study data from low-, middle- and high-income countries[20]. This analysis found no association between spirometric obstruction and self-reported use of solid fuels for cooking or heating. This is, however, an area of controversy with investigators disagreeing about the interpretation of the available data[21,22].

Many of the studies conducted to date looking at the association between COPD and exposure to household air pollution have had important methodological limitations including case definition and exposure assessments. So far, studies of the long-term effects of air pollution have had to use a self-reported history of exposure with all the limitations that this may imply. To improve exposure assessment, we included 48 hours of personal air pollution exposure measurements in study participants in addition to questionnaire-based exposure assessments. Whilst this approach and the particular devices used have their limitations, by doing this we were able to deliver the first study of the burden of non-communicable lung disease anywhere in the world to incorporate BOLD study methodology.
and measurements of personal air pollution exposure and to do so in almost 1000 participants.

Although personal air pollution exposure levels were undoubtedly high and at levels at which adverse health effects would be expected, and although widely considered a risk factor for non-communicable respiratory diseases and COPD in particular, the only respiratory outcome associated with measured exposure to PM$_{2.5}$ or CO was ‘any chronic respiratory symptoms’ with increased CO exposure. Interestingly, whether questionnaire-based or directly measured personal air pollution exposure assessments were used, there was no significant association between air pollution exposure and an increased risk of spirometric abnormalities. However, we acknowledge that 48-hour measurements of air pollutants may not be an adequate surrogate for cumulative exposure to household air pollution that has been associated, albeit by self-report, with COPD. Our observations, taken together with the findings of other recent studies, bring into question the extent to which household air pollution and other sources of air pollution play in the development of abnormal lung function in rural African settings like this one in rural Malawi. It is plausible that the levels of personal exposure to air pollution seen are not high enough to accelerate lung function decline and the development of airflow obstruction in the way that tobacco smoke does; a prospective cohort study of the rate of decline in lung function in relation to air pollution exposures is needed in adults in sub-Saharan Africa to explore this further.

This study benefited from being conducted at the same time and in the same villages as CAPS which presented the opportunity to look for an effect of the CAPS intervention on respiratory symptoms, spirometric indices and personal air pollution exposures in a subsample of adults. Consistent with the main trial findings of no effect of the intervention on pneumonia in children under the age of 5,[5] we found no evidence that the intervention was associated with beneficial effects on any of these trial secondary outcome measures amongst adults. However, these analyses were exploratory secondary analyses limited by a relatively small number of participants and therefore statistical power to detect effects and, whilst sufficient to see an effect on symptoms and air pollution exposures, there was limited time between intervention and outcome assessment for potential effects on spirometric indices to be seen. Other possible explanations for the lack of effect of the CAPS
intervention on these outcomes include insufficient levels of intervention adoption, insufficient reductions in emissions and exposures, and other sources of air pollution exposure overwhelming any potential effect of the intervention[5].

A notable observation of this study was that 35% of participants had spirometric restriction when benchmarked against NHANES III Caucasian reference range values. We consider the approach we have taken of benchmarking against the NHANES III Caucasian reference ranges as the best we can do at this point in time whilst accepting that this and all other currently available alternatives are not ideal. That includes locally-derived reference ranges that might be helpful in defining what is ‘usual’ lung function in asymptomatic non-smoking Malawian adults but which may be far from ‘optimal potential normal lung function’. Since there is evidence that the prognostic significance of spirometric restriction holds irrespective of racial/ethnic group when benchmarked in this way[23,24], the finding of such a high burden of spirometric restriction in the rural Malawian population, and elsewhere in sub-Saharan Africa [25,26], is of considerable concern; observational cohort studies are needed to understand the clinical characteristics and prognostic significance of these findings. The underlying drivers of spirometric restriction in sub-Saharan African populations are not yet understood but we hypothesise that these are primarily environmental insults experienced in early life – e.g. malnutrition, infections and air pollution exposures pre-conception, in-utero and during childhood – such that adulthood is reached without maximal potential lung function having been achieved. Cross-sectional studies of the burden and determinants of non-communicable lung disease in children in sub-Saharan Africa are needed to explore whether the same patterns of abnormality are seen in early life and, if so, studies even earlier in the life course to identifying potential windows of opportunity to intervene to maximise lung health.

Strengths of this study include that it was conducted in a highly challenging research setting in one of the world’s poorest rural communities as part of the CAPS protocol; it is the first of the global BOLD studies to be conducted in a rural sub-Saharan African setting; and it is also the first BOLD study to incorporate personal air pollution exposure measurements and to do so at scale. Limitations include questionnaire assessments for most variables with potential for recall bias, the potential bias (e.g. under-estimation of the burden of spirometric
abnormalities) caused by participants who did not do spirometry although the quality of those that did spirometry was generally high; and air pollution exposure assessments that provided only a 48-hour snapshot of exposure and were based on a light-scattering method alone for PM$_{2.5}$.

In conclusion, we found that exposures to air pollution among Malawian adults living in communities participating in CAPS were at levels well beyond those considered safe by the WHO. In keeping with the primary outcome of the CAPS trial, we found no effect of the intervention on any of the secondary trial outcomes – respiratory symptoms, spirometric indices or air pollution exposures – in the sub-sample of adults participating in both this study and the trial. The prevalence of chronic respiratory symptoms and abnormal spirometry suggests that there may be an important burden of non-communicable respiratory disease in these communities. The characteristics of non-communicable respiratory disease in sub-Saharan Africa may be different to those previously expected with more spirometric restriction and less obstruction (and household air pollution-associated COPD) than has been thought to exist. There is a need to explore other plausible explanations for the poor lung function observed in these and other low- and middle-income country populations including further exploration of the role of tuberculosis, recurrent pneumonia, and nutrition. Clinically- and cost-effective approaches for the prevention and control of non-communicable respiratory diseases are very much needed in sub-Saharan Africa.
4.11 References

12. www.thelancet.com/protocol-reviews/13PRT-4689


Chapter 5: Non-Communicable Respiratory Disease in Malawi: a Systematic Review and Meta-Analysis

5.1 Chapter Layout

This chapter is presented as a Word version of the manuscript accepted for publication by the journal. The tables and figures which were submitted to the journal as a separate document have been inserted into the text. There was not an online supplement for this paper, but the final published PDF can be found in the Appendix for Chapter 5 Section 1.

5.2 My Contribution to the Paper

I co-wrote the protocol for this systematic review with Dr Hannah Jary. I was the second reviewer on the initial systematic search. After a significant logistical delay, I took on completion of a second search to extend the original search performed by Dr Jary at an earlier time point). I performed the data extraction alongside Dr Jary. I did the analysis and completed all the main tables myself, and Dr Lesosky oversaw the analysis and provided significant assistance with coding to produce Figures 2 and 3. I wrote the final draft, co-ordinated all the co-author comments, and performed the final editing. Prof. Kevin Mortimer is named as the corresponding author for logistical reasons, but I completed the submission and publication process and made all the amendments requested by the editor of the journal.

5.3 Contribution of Other Authors to the Paper

<table>
<thead>
<tr>
<th>Name</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Hannah Jary</td>
<td>Wrote the initial protocol with my input, completed initial search process, read and commented on the final draft</td>
</tr>
<tr>
<td>Dr Jamilah Meghji</td>
<td>Read and commented on the final draft</td>
</tr>
<tr>
<td>Dr Sarah Rylance</td>
<td>Read and commented on the final draft</td>
</tr>
<tr>
<td>Dr Jones Masiye</td>
<td>Provided agreement and advise from the Malawi Ministry of Health. Dr Masiye is a key player in policy making for NCD in Malawi. Read and agreed final draft.</td>
</tr>
<tr>
<td>Dr Hasting Chiumia</td>
<td>Provided agreement and advise from the Malawi MOH, Dr Chiumia is a key player in policy making for NCD in Malawi. Read and agreed final draft.</td>
</tr>
<tr>
<td>Dr Jamie Rylance</td>
<td>Primary PhD supervisor. Read and commented on versions of the paper.</td>
</tr>
</tbody>
</table>
Prof Kevin Mortimer | PhD supervisor, provided overall senior support for this systematic review, read and commented on all versions of the paper.

Dr Maia Lesosky | Provided an independent review for data extraction and second reviewer for the second search (due to Dr Jary being on maternity leave), provided statistical oversight and helped with the coding to produce figure 2 and 3. Read and commented on the methods section for the final draft.

5.4 This Paper as Part of the Thesis

Having completed the rural BOLD and CAPS analysis reported in Chapter 4, it became clear that there was a high burden of abnormal spirometry seen in Chikwawa (rural Malawi). However the burden of disease across the country was not known. An estimation of the burden of non-communicable respiratory disease in Malawi would be beneficial to the Malawi Ministry of Health (MOH) and would highlight gaps in the literature within Malawi.

I have built skills as a researcher by using this systematic review methodology, having already completed a quantitative analysis of longitudinal data (Chapter 2), qualitative research (Chapter 3) and a cross-sectional study (Chapter 4).
Non-communicable respiratory disease in Malawi: a systematic review and meta analysis

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Authors contributions

Design: RN, HJ, JR, KM, ML
Acquisition of data: RN, HJ, ML
Analysis of data: RN, HJ, JM, SR, JR, KM, ML
Interpretation of data: RN, HJ, JM, SR, JM, HC, JR, KM, ML
Writing the manuscript, approval of the version to be published and agreement to be accountable for all aspects of the work: All authors

Funding

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Word Count: 2670

Key Words: COPD, Asthma, Chronic lung disease, Cough, Non-communicable disease, Malawi
5.6 Abstract

**Background:** Non-communicable respiratory diseases are important contributors to morbidity and mortality in sub-Saharan African countries like Malawi.

**Aim:** To conduct a systematic review of the available literature of chronic respiratory disease in Malawi.

**Methods:** We conducted a systematic protocol-driven literature search of key scientific databases including Scopus and Medline. Papers were independently assessed for eligibility by two authors and included if they reported objective measures (including self-reported standard symptoms) of chronic respiratory disease and were conducted in Malawi. A meta-analysis of available estimates was conducted and we re-analysed data from three of these studies in a secondary data analysis to allow between-study comparisons.

**Results:** Our search identified 393 papers of which 17 (5 child and 12 adult) met the inclusion criteria. Wheeze was the symptom most frequently reported in children in community (12.1%), hospital (11.2%) and HIV clinic (8.1%) settings. Cough was the symptom most frequently reported in adults in the community (3-18%). Spirometric abnormalities varied substantially between studies *e.g.* in adults, airflow obstruction varied between 2.3% and 20% and low FVC between 2.7% and 52.8%.

**Conclusion:** We found a high burden of chronic respiratory symptoms and abnormal spirometry (particularly low FVC) within paediatric and adult populations in Malawi. The estimates for country wide burden of disease were limited by the heterogeneity of the methods used to assess symptoms and spirometry. We need a better understanding of the determinants and natural history of non-communicable respiratory disease across the life-course in Malawi.
5.7 Introduction

Non-communicable diseases (NCDs) kill 41 million people globally, accounting for 71% deaths worldwide. More than three quarters (32 million) of these deaths occur in low- and middle-income countries (LMICs), including LMICs in sub-Saharan Africa like Malawi. Health policy has historically focussed on communicable rather than non-communicable disease in sub-Saharan African countries, although the need to prioritise NCD prevention and control is increasingly recognised, with the Malawi National Health Research Agenda highlighting that chronic lung disorders is a priority research area for the country.

Non-communicable respiratory diseases are major contributors to NCD mortality with 3.6 million attributable deaths globally in 2015. Of these diseases, asthma and chronic obstructive pulmonary disease (COPD) are the most common. The International Study of Asthma and Allergies in Childhood (ISAAC) estimated asthma prevalence using standardised questionnaires in 105 countries. In the seven countries from sub-Saharan Africa, prevalence varied between 9.1% in Ethiopia and 20.3% in South Africa. The prevalence of COPD has been estimated from cross-sectional spirometry-based studies, including the international Burden of Obstructive Lung Disease (BOLD) initiative. The highest prevalence was seen in Cape Town, South Africa where moderate to severe obstruction was present in 19.1% of the adult population whilst prevalence in Ile-Ife (Nigeria), urban Blantyre (Malawi) and rural Chikwawa (Malawi) were 7.7%, 3.6% and 8.7% respectively. Recently, two further studies have reported lower levels of obstruction in Uganda: 6.1% and 2% in rural populations and 1.5% in an urban population.

We conducted a systematic review and pooled analysis of the burden of and risk factors for non-communicable respiratory diseases in Malawi. This review focused on any population, any interventions, any comparison techniques used, any outcomes from studies and any study design.
5.8 Methods

Systematic Review
This systematic review is registered with the Centre for Reviews and Dissemination (Registration number: CRD42018117325). The full protocol is available at http://www.crd.york.ac.uk/prospero.

Eligibility criteria
Studies describing the burden of non-communicable respiratory diseases (including COPD, asthma, low Forced Vital Capacity (FVC)/restrictive disease and bronchiectasis) in Malawian individuals of any population (i.e. any sex or age), involving any intervention and outcomes linked to non-communicable respiratory disease. We included any study design in the searches. This included studies that defined non-communicable respiratory diseases using symptoms, self-reported diagnosis, doctor diagnosis and spirometry.

Search strategy
The databases and grey literature listed in Box 1 were searched using the search terms and Boolean phrases listed in Box 2 and the search strategy set out in Box 3. Identified papers were imported into EndNote X7. Reference lists of all selected papers were reviewed for any potentially eligible titles. For studies where relevant details were not available, authors were invited to supply information if their contact details were available.

Box 1: Databases and Grey Literature
Databases:
- Scopus (including EMBASE)
- MEDLINE (OVID)
- Web of Science
- Cochrane Central Register of Controlled Trials (CENTRAL)
- CINAHL (OVID)
- SciELO

Grey Literature:
- World Health Organization Clinical Trials Registry
- www.clinicaltrials.gov
- European Association for Grey Literature Exploitation (EAGLE)
- Experts in field
### Box 2: Search terms and Boolean phrases used

#### Outcomes (OR):
- “chronic respiratory” OR “non-communicable lung” OR “chronic obstructive pulmonary disease” OR “COPD” OR “asthma” OR “obstructive lung” OR “restrictive lung” OR “obstructive respiratory” OR “restrictive respiratory” OR “obstructive airway*” OR “restrictive airway*” OR “spirometr*” OR “wheeze” OR “chronic cough” OR “shortness of breath” OR “breathlessness” OR “chronic sputum”

AND

**Location:** “Malawi”

### Box 3: Example search strategy for Medline (OVID)

1. “chronic respiratory”.mp,tw.
4. COPD.mp,tw.
5. asthma.mp,tw.
10. “obstructive airway*”.mp,tw.
12. spirometr*.mp,tw.
13. wheeze.mp,tw.
15. “shortness of breath.mp,tw.
16. breathlessness.mp,tw.
17. “chronic sputum”.mp,tw.
18. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
19. Malawi.mp,tw.
20. 18 AND 19
Article Screening
Following removal of duplicates, all titles of identified papers were independently reviewed for eligibility by two authors (HJ & RN). Abstracts of the selected titles and then full text of the selected articles were independently reviewed for eligibility by two authors (HJ & RN), according to the selection criteria. Discordant decisions were resolved by discussion, with final arbitration by a third author.

Data extraction
Data were extracted by HJ and RN from the selected papers using a data extraction form, which were piloted first, from which summary tables and narrative synthesis were produced. ML independently checked the data extraction. We also collated information regarding household air pollution exposure, smoking and previous TB where available.

Methodological quality assessment
The methodological quality of studies was assessed by HJ using the Newcastle-Ottawa Scale for cohort and case-control studies (score out of 9) and a modified version of the Newcastle-Ottawa Scale for cross-sectional studies (score out of 5) (Table 1).

Statistical analysis
Published estimates of prevalence of symptoms, obstruction or low FVC, and mean (SD) and median (interquartile range (IQR)) carbon monoxide (CO), fine particulate matter (PM$_{2.5}$) were extracted for meta-analysis. Forest plots using the estimated proportion and 95% confidence intervals were plotted. Meta-analysis estimates of overall prevalence was stratified by age group (adult, paediatric) and estimated using the DerSimonian-Laird random effects model (R package metaviz) $^{19}$. Meta-analysis derived estimates were only calculated for outcomes in which the studies were deemed to be adequately homogenous. Estimates of measures of heterogeneity ($I^2$, $\tau^2$) and overall Q-test were generated using linear mixed effects models (R package metaphor) and reported. Assessment of publication bias was evaluated by visual inspection of funnel plots.

Data from three of the studies included in the meta-analysis that had been done to the same core BOLD protocol were re-analysed in order to provide comparable estimates: the Adult Lung Health Study (ALHS); the Blantyre Health Study (BHS); and the Acute Infection of the Respiratory tract Study (AIR Study)$^{15,16,20}$. This allowed for a pooled analysis of data which had not previously been performed (referred to subsequently as the “pooled
analysis”) to distinguish this from the “meta-analysis”. Details of the sampling and measurement procedures for these three studies have been described previously so we restrict our description of methods to the secondary analysis presented here 12, 13, 15, 16, 20, 21. Prevalence (SD) of symptoms, exposures, obstruction and low FVC were estimated using the combined three data sources, termed “pooled data” below. Median (IQR) for CO and PM$_{2.5}$ exposure estimates were calculated.

**Ethics**

Liverpool School of Tropical Medicine gave ethical approval for all three studies which we included for secondary data analysis (#12.08, #12.40 and #14.016). ALHS and AIR were approved by the College of Medicine Research and Ethics Committee, Malawi (p.11/12/1308 and P.02/14/1518, respectively), and BHS was approved by the National Research and Ethics Committee of Malawi (12.08). All participants of these studies provided informed consent.
5.9 Results

Study Selection
Database and grey literature searches done on 9 October 2018 and updated on 3rd June 2019 identified 393 titles for review of which 17 papers met the inclusion criteria (Figure 1). Funnel plots were limited by the small number of studies but were relatively symmetrical (Eager test p=0.017 for obstruction and p=0.032 for restriction) (Figure 2).

Quality assessment
The included studies were of variable quality, with studies specifically designed to assess the burden of non-communicable respiratory disease being of the highest quality (Table 1).

Study characteristics
The studies included used cohort (n=1), case-control (n=1) and cross-sectional (n=15) study designs (or included a cross-sectional description of non-communicable respiratory disease burden nested within a Randomised Control Trial or economic evaluation) (Table 2). Five studies reported on paediatric populations, while twelve reported on adult populations, with one of these studies including a population from 10-65 years (Table 2). Nine studies were from urban settings only (four healthcare or clinic-based, three community-based and the case-control and cohort studies were done in both community and health care settings), five were from rural settings only (all community-based), and three studies spanned both rural and urban settings (all community-based).
Figure 1: PRISMA Flow Chart

```
Database searches
465

Grey Literature and Expert Knowledge
4

Duplicate removal 76

Total for Title Review
393

Titles Rejected 344

For Abstract Review
125

Abstracts Rejected 86

Abstracts Not Found 1

For Paper Review
38

Papers Rejected 19

Papers Not Found 2

Selected Papers
17

identified from reference lists 76

Review of reference lists of review papers

Review of reference lists of review papers

Review of reference lists of selected papers
```

Figure 1: PRISMA Flow Chart depicting the inclusion and inclusion of studies. Reasons for abstract rejection: no primary data (45), no Malawian data (26), no assessment of non-communicable lung disease (12), duplicate data (2), data not yet available (1). Reasons for paper rejection: no Malawian data (9), duplicate data (6), no assessment on non-communicable lung disease (2), data not yet available (1), no primary data (1).
Figure 2: Funnel plots for lung function estimates in paediatric (blue) and adult (red) populations. Panel A (left): restriction, Panel B (right) obstruction.

Table 1: Summary of risk of bias assessment: Newcastle-Ottawa Scale

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection (out of 4)</th>
<th>Comparability (out of 2)</th>
<th>NCLD assessment (out of 3)</th>
<th>Overall Score (out of 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jary et al, 2017</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Lelijveld et al, 2017</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection (out of 3)</th>
<th>NCLD assessment (out of 2)</th>
<th>Overall Score (out of 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zverev et al, 2001</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Fullerton et al, 2011</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>To et al, 2012</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Cook et al, 2013</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Jary et al, 2014</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Manjomo et al, 2016</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Meghji et al, 2016</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Mwalukomo et al, 2016</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Wang et al, 2016</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Banda et al, 2017</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Das et al, 2017</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Townend et al, 2017</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cohen et al 2019</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Nightingale et al, 2019</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Rylance et al, 2019</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

NCLD: non-communicable lung disease.
Symptoms
Thirteen studies assessed self-reported respiratory symptoms or diagnoses using questionnaires, of which five used BOLD questionnaires \(^{15, 16, 20, 23, 24, 26-29, 31-34}\) (Table 3).

In the paediatric population, the most commonly reported symptom in the community was wheeze, with a prevalence of 12.1%, followed by cough (prevalence 8%) \(^{24}\). In the two studies of symptom prevalence in hospital clinics, cough was more common (41.7% and 37.5%) than wheeze (11.2% and 8.1%) \(^{23, 24}\). The meta-analysis estimate for prevalence of cough symptoms in children was 29.1 (SE 10.6, \(p = 0.0059, I^2 = 98\%\), Q-test \(p < 0.0001\)) (Figure 3).

Amongst adult populations in the community, cough was the most reported symptom (range 3-18.6%), followed by shortness of breath (range 1.6-13%). Productive cough and phlegm production were less commonly reported (range 0.2-9% and 1.4-5.9% respectively). The meta-analysis and pooled analysis estimates for prevalence of cough symptoms in adults were 13.3 (SE: 10.6, \(p < 0.0001, I^2 = 93\%\), Q-test \(p < 0.0001\)) and 10.7%, respectively (Figure 3).

Lung Function
Eight of the nine studies (four paediatric and four adult) that performed spirometry reported data collected to American Thoracic Society (ATS)/European Respiratory Society (ERS) standards. However, five different ranges were used and a mix of raw values, percentage predicted values and Z-scores were used in analysis \(^{20, 23-27, 33-35}\) (Table 4).

One study - a community-based cross-sectional study - focused on Peak Expiratory Flow Rate (PEFR) in stunted children, finding reduced PEFR in those with poor growth \(^{20}\). In paediatric community populations, 6.6 to 9.0% of the population had obstruction and 6.6 to 7.5% had low FVC. In those with sickle cell disease and HIV infection, obstructive spirometry was identified in 0 and 18%, and low FVC in 25% and 17% using local reference ranges (58% and 20% using international reference ranges), respectively \(^{23, 24}\). The cohort study that assessed lung function in malnourished children found reduced FEV\(_1\) and FVC in all study groups, but with no significant difference between paediatric survivors of severe acute malnutrition and healthy controls \(^{25}\). Asthma diagnosis based on spirometry and questionnaires in children was reported in 3.9% of the community or 12.1% if wheeze was
used as the definition, and also reported in 4.2% of children with sickle cell anaemia\textsuperscript{23, 26}. No studies used the same definition for asthma in the same way.

The range of obstruction reported in adults where spirometry had been completed was 2.3% to 20% with low FVC varying from 2.7% to 52.8% \textsuperscript{20, 27}. Using different ranges within the same population resulted in a prevalence of obstruction of 2.3 to 4.2% and low FVC of 9% to 38.6% using local and NHANES Caucasian ranges respectively \textsuperscript{15, 16}. The prevalence of asthma in adults ranged between 0-12.2% with a mix of doctor diagnosis (7.6 -12.2%), self-reported (4.7-8%) and spirometry diagnosed (0- 4.2%) \textsuperscript{16,18,25,26,28,30-32}. In meta-analysis, the prevalence of obstruction in adults was 8.3% (SE 2.4, $p = 0.0007$, $I^2 = 89\%$, Q-test $p < 0.0001$), and low FVC 31% (SE 7.2, $p < 0.0001$, $I^2 = 97\%$, Q-test $p < 0.0001$ (Figure 2). The pooled analysis estimated overall FEV\textsubscript{1} 2.64L (0.69), FVC 3.28L (0.77) and FEV\textsubscript{1}/FVC 80.5% (8.48). The pooled prevalence of obstruction was 8.4% and low FVC was 37.5% (NHANES) or 16.3% (local range).

**Risk Factors**

The most common risk factors for non-communicable respiratory disease reported were biomass fuel use and smoking. Biomass fuel exposure was assessed in different ways in different studies. In paediatric studies biomass exposure varied from 14%-83% of the study population \textsuperscript{23, 25} (Table 3). In adult studies, self-reported biomass exposure ranged from 51% to 100% \textsuperscript{29, 34}. Self-reported smoking prevalence (“ever smoked”) ranged from 1-28.2% in the adult population \textsuperscript{27, 30}. Previous TB and low BMI were considered possible risk factors in the BOLD studies. Meta-analysis and pooled analysis of associations between risk factors and lung function was not possible due to incomplete reporting across studies \textsuperscript{15, 16, 20, 34}. 
Figure 3: Forest plots and meta-analysis estimates for symptoms (Panel A–D), exposures (Panel E, F) and respiratory outcomes (panel G, H).

A: Cough
B: Wheeze
C: Phlegm
D: SOB

E: Smoke Exposure
F: Biomass Exposure
G: Obstruction
H: Restriction
### Table 2: Summary of main paper findings (Date order)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Rural/Urban</th>
<th>Mean Age (y)</th>
<th>Setting and Study Design</th>
<th>Sample Size</th>
<th>Assessment Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zverev</td>
<td>2001</td>
<td>Urban</td>
<td>Children in primary school, children from each class were randomly selected</td>
<td>539</td>
<td>Peak expiratory flow only. No symptoms questionnaires. No spirometry</td>
<td></td>
</tr>
<tr>
<td>Cook</td>
<td>2013</td>
<td>Urban Clinic</td>
<td>11.5</td>
<td>Consecutive recruitment from paediatric Sickle Cell Anaemia Clinic</td>
<td>25</td>
<td>Self-reported respiratory symptoms (ISAAC questionnaire) and spirometry</td>
</tr>
<tr>
<td>Mwalukomo</td>
<td>2016</td>
<td>Urban Clinic</td>
<td>11.1</td>
<td>First 3 eligible patients at paediatric HIV clinic per day were recruited.</td>
<td>160</td>
<td>Self-reported respiratory symptoms and clinical observation and Spirometry</td>
</tr>
<tr>
<td>Lelijveld</td>
<td>2017</td>
<td>Urban Hospital</td>
<td>Cases: consecutive patients admitted with Severe Acute Malnutrition in 2006-2007. Sibling controls: closest in age to case. Community controls: random direction selected from case home then door-to-door recruitment (age- &amp; sex-matched).</td>
<td>320 cases (of 477 alive 1 year post original discharge); 217 sibling controls; 184 community controls</td>
<td>Spirometry</td>
<td></td>
</tr>
<tr>
<td>Rylance</td>
<td>2019</td>
<td>Rural</td>
<td>7.1</td>
<td>Population sampling with control and intervention arm</td>
<td>804 cases (260 intervention control) from CAPS households</td>
<td>Self-reported respiratory symptoms (BOLD questionnaire) and spirometry</td>
</tr>
</tbody>
</table>

### Adult

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Rural/Urban</th>
<th>Mean Age (y)</th>
<th>Setting and Study Design</th>
<th>Sample Size</th>
<th>Assessment Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fullerton</td>
<td>2011</td>
<td>Rural/urban</td>
<td>39</td>
<td>Cross-sectional survey. Rural: first household semi-randomly selected, then snowballing sampling strategy. Urban: randomly selected from 360 research volunteers, then snowballing sampling strategy. Biased selection toward women</td>
<td>374</td>
<td>Self-reported respiratory symptoms and diagnoses and Spirometry</td>
</tr>
<tr>
<td>To</td>
<td>2012</td>
<td>Rural/Urban</td>
<td></td>
<td>Multi stage cluster design: random</td>
<td>3890</td>
<td>Self-reported respiratory symptoms and diagnoses and Self-reported doctor diagnosed.</td>
</tr>
<tr>
<td>Jary</td>
<td>2014</td>
<td>Rural</td>
<td>35</td>
<td>Community based survey of women wishing to purchase a cookstove – not randomly selected.</td>
<td>51</td>
<td>Self-reported respiratory symptoms.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Setting</td>
<td>Methodology</td>
<td>Sample Size (Eligible)</td>
<td>Data Collection Means</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
<td>---------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Meghji ^</td>
<td>2016</td>
<td>Urban</td>
<td>Random sample from enumerated population – age- and sex-stratified population-representative sample.</td>
<td>1059 (of 1240 eligible)</td>
<td>Self-reported respiratory symptoms (BOLD questionnaire) and spirometry.</td>
<td></td>
</tr>
<tr>
<td>Manjomo</td>
<td>2016</td>
<td>Urban</td>
<td>All patients registered with NCDs attending a chronic care clinic at a primary health care centre.</td>
<td>1135</td>
<td>Diagnosis of asthma at clinic.</td>
<td></td>
</tr>
<tr>
<td>Wang</td>
<td>2016</td>
<td>Rural</td>
<td>Cross sectional survey, from three districts. Sampling method unclear. Paediatric adult overlap with participant 10-65 years old.</td>
<td>5643 individuals from 1199 households</td>
<td>Self-reported chronic respiratory symptoms reported as a group.</td>
<td></td>
</tr>
<tr>
<td>Banda</td>
<td>2017</td>
<td>Rural</td>
<td>Population proportional sampling using electronic satellite maps: 30 villages randomly selected from each cluster (27 health centre catchment population), 7 households randomly selected from each village.</td>
<td>15795 individuals from 6304 households with 1728 who had health passports checked for symptoms</td>
<td>Self-reported respiratory symptoms / health passport assessment of symptoms.</td>
<td></td>
</tr>
<tr>
<td>Das</td>
<td>2017</td>
<td>Rural/peri-urban</td>
<td>Random sample of households from representative villages.</td>
<td>655 households (382 rural, 273 peri-urban).</td>
<td>Self-reported respiratory symptoms.</td>
<td></td>
</tr>
<tr>
<td>Jary</td>
<td>2017</td>
<td>Urban</td>
<td>Cases: all hospitalised pneumonia cases. Controls: randomly generated GPS coordinates used to select participant households, one individual per household randomly selected (frequency matched for age and sex to cases, stratified by HIV status).</td>
<td>Cases: 145 (of 428 recruited). Controls: 253 (of 300 recruited).</td>
<td>Self-reported respiratory symptoms and diagnoses (BOLD questionnaire) and Spirometry.</td>
<td></td>
</tr>
<tr>
<td>Townend ^</td>
<td>2017</td>
<td>Urban</td>
<td>Random sample from enumerated population – age- and sex-stratified population-representative sample.</td>
<td>402 (of 758 eligible)</td>
<td>Self-reported respiratory diagnoses (BOLD questionnaire).</td>
<td></td>
</tr>
<tr>
<td>Cohen</td>
<td>2019</td>
<td>Urban</td>
<td>All patient in a 15 month period having TB retreatment at Blantyre hospital and over the age of 16</td>
<td>103 (of an eligible 158)</td>
<td>Spirometry CT scans at 2 months in treatment but not included in this review as still deemed acute.</td>
<td></td>
</tr>
<tr>
<td>Nightingale</td>
<td>2019</td>
<td>Rural</td>
<td>Random sample from enumerated population – age- and sex-stratified population-representative sample.</td>
<td>1481 (of 3000 attempted to contact).</td>
<td>Self-reported respiratory symptoms (BOLD questionnaire) and spirometry.</td>
<td></td>
</tr>
</tbody>
</table>

^ from the same study population.
Table 3: Extracted percent symptoms and specific exposures where reported. Empty cells indicate not reported.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Symptoms (percent)</th>
<th>Exposures (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cough</td>
<td>Wheeze</td>
</tr>
<tr>
<td>Zverev at al 2001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cook 2013</td>
<td>41.7</td>
<td>11.2</td>
</tr>
<tr>
<td>Mwalukomo 2016</td>
<td>37.5</td>
<td>8.1</td>
</tr>
<tr>
<td>Lelijveld 2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rylance 2019</td>
<td>8</td>
<td>12.1</td>
</tr>
<tr>
<td>Fullerton 2011</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>To 2012</td>
<td></td>
<td>7.8</td>
</tr>
<tr>
<td>Jary 2014</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td>Meghji 2016*</td>
<td>7.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Manjomo 2016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al 2016</td>
<td>2.0^^^^</td>
<td></td>
</tr>
<tr>
<td>Banda 2017</td>
<td>18.6</td>
<td>5.9</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>10.7</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>Das 2017</td>
<td></td>
<td>17.3</td>
</tr>
<tr>
<td>Jary 2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Townend 2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohen 2019</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nightingale 2019</td>
<td></td>
<td>11.1</td>
</tr>
<tr>
<td>Secondary analysis from Malawi pooled data 2019</td>
<td></td>
<td>10.7</td>
</tr>
</tbody>
</table>

^ Open fire for > 20 years  ^^ Africa region estimate ^^^Chronic symptoms combined  * indoor tobacco/biofuel use
Table 4: Summary extracted spirometry (FEV1, FVC) or obstruction/Low FVC where available. Blank cells indicated not reported.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Group/subgroup</th>
<th>Asthma (%)</th>
<th>Low FVC (%)</th>
<th>Obstruction (%)</th>
<th>Reference range</th>
<th>FEV1, L Mean (SD)</th>
<th>FVC, L Mean (SD)</th>
<th>FEV1/FVC % Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zverev et al 2001</td>
<td>School Children</td>
<td>-</td>
<td>25</td>
<td>0</td>
<td>Local</td>
<td>1.45 (0.54)</td>
<td>1.68 (0.58)</td>
<td>86 (2.09)</td>
</tr>
<tr>
<td>Cook 2013</td>
<td>Clinic</td>
<td>-</td>
<td>25</td>
<td>0</td>
<td>Local</td>
<td>1.45 (0.54)</td>
<td>1.68 (0.58)</td>
<td>86 (2.09)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>58</td>
<td>0</td>
<td>Wang</td>
<td>-1.64*</td>
<td>-1.49*</td>
<td>-0.39*</td>
<td></td>
</tr>
<tr>
<td>Mwalukomo 2016</td>
<td>Clinic - HIV infected</td>
<td>-</td>
<td>20</td>
<td>17.9</td>
<td>GLI</td>
<td>-1.31*</td>
<td>-0.89*</td>
<td>-0.27*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17.2</td>
<td>12.4</td>
<td>GLI</td>
<td>-1.31*</td>
<td>-0.89*</td>
<td>-0.27*</td>
<td></td>
</tr>
<tr>
<td>Lelijveld 2017</td>
<td>Cases – clinic</td>
<td>-</td>
<td>20</td>
<td>17.9</td>
<td>GLI</td>
<td>-1.31*</td>
<td>-0.89*</td>
<td>-0.27*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17.2</td>
<td>12.4</td>
<td>GLI</td>
<td>-1.31*</td>
<td>-0.89*</td>
<td>-0.27*</td>
<td></td>
</tr>
<tr>
<td>Rylance 2019</td>
<td>Intervention</td>
<td>4.2</td>
<td>6.6</td>
<td>6.6</td>
<td>GLI</td>
<td>-0.41 (0.92)*</td>
<td>-0.22 (0.77)*</td>
<td>-0.4 (0.91)*</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>4.6</td>
<td>9.0</td>
<td>7.5</td>
<td>GLI</td>
<td>-0.60 (0.97)*</td>
<td>-0.44 (0.98)*</td>
<td>-0.34 (0.93)*</td>
</tr>
<tr>
<td></td>
<td>Population</td>
<td>3.9</td>
<td>6.3</td>
<td>7.1</td>
<td>GLI</td>
<td>-0.48 (0.93)</td>
<td>-0.30 (0.96)</td>
<td>-0.38 (0.90)</td>
</tr>
<tr>
<td>Fullerton 2011</td>
<td>Charcoal users</td>
<td>7</td>
<td>2.7</td>
<td>13.6</td>
<td>Knudsen &amp; asthma self reported</td>
<td>2.78 (0.68)</td>
<td>3.49 (0.87)</td>
<td>79.8 (7.5)</td>
</tr>
<tr>
<td>To 2012</td>
<td>Population</td>
<td>4.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jary 2014</td>
<td>Women cooking on cookstoves</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Population Reporting</td>
<td>Population</td>
<td>Nin</td>
<td>NHANES</td>
<td>Nin</td>
<td>Local</td>
<td>NHANES</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------</td>
<td>------------</td>
<td>-----</td>
<td>--------</td>
<td>-----</td>
<td>-------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>Meghji 2016</td>
<td>4.2</td>
<td>38.6</td>
<td>4.2</td>
<td>NHANES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manjomo 2016</td>
<td>Clinic</td>
<td>12.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al 2016</td>
<td>Population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Banda 2017</td>
<td>Population reporting respiratory symptoms</td>
<td>7.6</td>
<td>0.15</td>
<td>Medical Diagnosis only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Das 2017</td>
<td>Women cooking on biomass</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jary 2017</td>
<td>Cases – clinic</td>
<td>0</td>
<td>52.8</td>
<td>20</td>
<td>NHANES</td>
<td>2.73 (0.69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>controls</td>
<td>0</td>
<td>37.5</td>
<td>7.6</td>
<td>NHANES</td>
<td>2.48 (0.68)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Townend 2017</td>
<td>Population</td>
<td>5</td>
<td></td>
<td>NHANES</td>
<td>78 (8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohen 2019^</td>
<td>TB re treatment patients at hospital</td>
<td>19.4</td>
<td>5.83</td>
<td>NHANES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nightingale 2019</td>
<td>Population</td>
<td>34.8</td>
<td>8.7</td>
<td>NHANES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary analysis from Malawi pooled data 2019</td>
<td>Population</td>
<td>16.3 (Local)</td>
<td>37.5 (NHANES)</td>
<td>8.4</td>
<td>NHANES</td>
<td>2.64 (0.69)</td>
<td>3.28 (0.77)</td>
<td>80.5 (8.48)</td>
</tr>
</tbody>
</table>

* Z score, + Percentage predicted ^ Data only used from 8 months post TB
^ Only for moderate/severe obstruction
5.10 Discussion

We conducted a systematic review, secondary data analysis, and meta-analysis of studies of non-communicable respiratory disease in Malawi. We found 17 papers of variable quality with a Newcastle-Ottawa scale score ranging from 0-7 \textsuperscript{15, 16, 20, 22-34}. Five studies were in paediatric and 12 in adult populations. In paediatrics, we found the main symptom was wheeze with low FVC being reported in 6.3-20% of the population and obstruction in 7.1-17.9% \textsuperscript{22-26}. In adults, we found a high burden of lung disease, with cough being the most reported symptom. In studies that used spirometry as an outcome measure over 40% of the population had abnormal spirometry \textsuperscript{15, 16, 20, 27}. Low FVC was the most common abnormal spirometry finding with a pooled population estimate of 37.5% using NHANES Caucasian reference ranges. We found high usage of biomass fuel (50-100%) and a smoking prevalence of 1-21\% \textsuperscript{27, 29, 30, 34}.

Few studies have reported chronic respiratory symptoms and spirometry from sub-Saharan African populations. However, available findings from this Malawi-focused systematic review and meta-analysis are consistent with data from other sub-Saharan African countries. Data from the ISAAC study sites suggest wheeze in 5-16\% of children in sub-Saharan Africa, with nearly a half of them having severe symptoms \textsuperscript{11}. Globally the reporting of wheeze varies from 0.8 to 32.6\% in young children (age 6-7 yrs) and 2.4-37.6\% in older children (age 13-14 yrs)\textsuperscript{11}. In adults, cough was the most common symptom seen through the studies in sub-Saharan Africa, with BOLD studies in Nigeria reporting a prevalence of cough of 9.7\%\textsuperscript{36}. The prevalence of obstruction was lower than found in both Cape Town (19.1\%) and in rural Uganda (16.2\%), although tobacco smoking was more common in both these populations than in Malawi \textsuperscript{13, 37}. Two recent studies from Uganda found a prevalence of obstruction between 2 and 6.1\% and 2\% in a rural setting and 1.5\% in an urban setting which is more in keeping with the estimates seen in this review\textsuperscript{18, 17}. The high prevalence of low FVC seen in Malawi was similar to that seen in Nigeria and other resource-poor settings. There is limited literature about the possible causes of low FVC in adults in sub-Saharan Africa \textsuperscript{36}.

The strengths of this study are that it is the first systematic review and meta-analysis of chronic non-communicable respiratory disease in Malawi and adds to a growing body of
evidence highlighting the high burden of lung disease seen within Malawi and the wider sub-Saharan African region. It brings together studies of paediatric and adult populations from diverse settings in Malawi and includes a secondary analysis of data in order to provide new pooled burden of disease estimates. The estimates within this paper are limited by inconsistent methodologies. The studies we reported have been carried out across a range of populations, from the community setting to subgroups within an acute clinic. Paediatric data are particularly limited with only one paediatric study reporting lung function in community settings and the rest in specific populations like children with sickle cell disease. Symptoms were not reported in a consistent or standardised manner. Cough, wheeze, exertional dyspnoea and sputum production were the most common symptoms reported but there was widespread inconsistency in the definitions of these symptoms. All symptoms were self-reported; in studies without other diagnostic tools, this reduces the specificity of diagnosis. Diagnosis of COPD and asthma were made using a mix of clinical or self-reported diagnosis and spirometry. This is likely to explain the wide variation seen in categorising the burden of disease in Malawi. All spirometry was reported as completed to ATS standards. However, studies used different interpretative strategies with raw FEV1 and FVC being most common in the adult population and z-scores in the paediatric population. This lack of standardised reporting also adds uncertainty to estimation of the burden of disease in Malawi, and results in high heterogeneity in the meta-analysis estimates. As there is no validated spirometry reference range for sub-Saharan African populations, a variety of reference ranges were used in the studies reported here: the majority of paediatric studies used GLI (Global Lung Function Initiative) reference ranges and the majority of adult studies used NHANES Caucasian reference ranges. Use of NHANES Caucasian reference ranges has limitations including likely overestimation of the prevalence of low FVC but allows for comparison with other studies including BOLD studies (the largest, multi-national study of spirometric findings to date). Some studies have also published results interpreted with local (unvalidated) reference ranges.

Conclusion

In conclusion, we found a high burden of chronic respiratory symptoms and abnormal spirometry (particularly low FVC) in children and adults in Malawi. The estimates for country wide burden of disease were limited by the heterogeneity of the methods used to assess
symptoms and spirometry. Little is known about the determinants and natural history of non-communicable respiratory disease across the life course in Malawi. We suggest that non-communicable respiratory disease should be a priority for future research in Malawi and that this would benefit from the use of methodologies standardised across studies – for example by standardising diagnostic definitions and reporting spirometry to ATS/ERS standards. A consensus on the spirometry reference ranges used, or development of locally appropriate specific reference ranges, is needed. The substantial burden of chronic respiratory symptoms and abnormal spirometry in Malawian children and adults occurs in the context of health systems that need strengthening to provide high quality, accessible and affordable care for this population and has implications for Malawian policy- and decision-makers and the achievement of Universal Health Coverage in Malawi. Although deliberately focused on Malawi, the findings of this systematic review and meta-analysis will likely have generalisable relevance to the wider sub-Saharan African region.
5.11 References


Chapter 6: Respiratory Symptoms and Lung Function in Patients Treated for Pulmonary Tuberculosis in Malawi: A Prospective Cohort Study

6.1 Chapter Layout

This paper is presented as it was submitted for publication in Word format. As with other chapters the tables and figures have been inserted into the text for ease of reading. The supplement to this paper can be found in the Appendix for Chapter 6 Section 1. The PDF is not yet available as this paper is submitted but still in peer review.

6.2 My Contribution to the Paper

This cohort was initially designed and recruited by Dr Jamilah Meghji. I acted as Principal Investigator for this research project after the completion of the first year of follow-up of the cohort, which involved obtaining new ethical approvals from the Malawi College of Medicine Research and Ethic Board (COMREC) and LSTM (the sponsor). The study protocols, questionnaires design and data capture tools used after the first year of follow-up were new, and all my own work. I trained the fieldwork team in Malawi and worked with the MLW team to set up the study. I monitored all data collection, undertook quality control visits to the study site and managed the data that was collected. I cleaned, analysed and interpreted all the data myself with supervisory input from Dr Jamie Rylance. The statistics were overseen by Dr Maia Lesosky who had input to the coding for Figures 2 and Table 5. Dr Lesosky discussed the other tables with me, but I did all the statistical coding and interpretation independently. I wrote the draft and completed all edits from the co-authors’ comments. I submitted the paper and have made all editorial changes requested by the journal.

6.3 Contribution of other authors to the paper

<table>
<thead>
<tr>
<th>Name</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mrs Beatrice Chinoko</td>
<td>Study nurse based in Malawi, co-ordinated the fieldwork team and managed all communication with me. Read and commented on the final draft paper.</td>
</tr>
<tr>
<td>Dr Maia Lesosky</td>
<td>Provided statistical support and helped with complex coding, read and commented on the final draft paper.</td>
</tr>
</tbody>
</table>
Dr Sarah Rylance
Provided managerial oversight to the fieldwork team at MLW when I was not the country, read and commented on the final draft paper.

Mr Bright Mnesa
Data manager in country and key person to allow communication between UK and Malawi. Read and agreed the final draft.

Dr Peter Banda
Provided medical support in Malawi and help with liaison between myself and Queen Elizabeth Central Hospital. Read and agreed the final draft.

Dr Elizabeth Jokes
Provided radiological support and interpretation of the year zero and year one x-ray and CT-scans. read and commented on the final draft paper.

Prof Bertie Squire
PhD supervisor for part of this study, collaborator in setting up the post-TB cohort in Malawi, senior member of the post-TB cohort working group. Read and agreed final the draft.

Prof Kevin Mortimer
PhD supervisor, collaborator is setting up the post-TB cohort in Malawi. Read and commented on all versions of the draft.

Dr Jamilah Meghji
Set up the Post-TB cohort in Malawi as part of her PhD and published the baseline and year one data. Read and commented on all versions of the draft and final paper.

Dr Jamie Rylance
Primary PhD supervisor, provided overall senior supervisory support. Provided overall medical support in Malawi. Read, commented on and discussed all stages of this paper.

6.4 This Paper as Part of the Thesis

Pulmonary tuberculosis (PTB) is strongly associated with people living in disadvantaged situations (such as poverty), and it is implicated in the development of chronic respiratory disease. In the cross-sectional study presented in Chapter 4, it was found that previous PTB was associated with chronic respiratory symptoms in a rural population in Malawi. Additional evidence from other BOLD study sites suggested previous PTB was associated with abnormal spirometry. This chapter allowed me to probe deeper into PTB as a possible risk for chronic respiratory disease and allowed me to apply skills I had learn in Chapter 2 to develop more complex multiple time point mixed effects models.
Respiratory symptoms and lung function in patients treated for pulmonary tuberculosis in Malawi: A prospective cohort study

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* Co-senior authors

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⁴ Department of Medicine, College of Medicine and Queen Elizabeth Central Hospital, Blantyre, Malawi

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We thank the NIHR Global Health Research Unit on Lung Health and TB in Africa at LSTM - “IMPALA” for helping to make this work possible. In relation to IMPALA (grant number 16/136/35) specifically: This research was funded by the National Institute for Health Research (NIHR) (IMPALA, grant reference 16/136/35) using UK aid from the UK Government to support global health research. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR or the UK Department of Health and Social Care.

This work was also supported by the MRC GCRF-funded project “Lung Health in Africa across the life course” (LuLi) [grant number MR/P022006/1]

The funders had no role in the study design, data collection, analysis, interpretation or writing of this report. The senior authors had full access to the study data and had final responsibility for the decision to submit for publication.

Acknowledgements

We would like to thank Joseph Jacob and Harmien Zonderland for their work interpreting the HRCT imaging, and Lindsay Zurba for double reading the spirometry traces. We would also like to thank Hygiene Kumwenda, Malumbo Ng’oma and Emma Nyirenda for their work in the field.
6.6 Abstract

**Rationale**

Pulmonary tuberculosis (PTB) can cause post-TB lung disease (PTLD) associated with respiratory symptoms, spirometric and radiological abnormalities. Understanding of the predictors and natural history of PTLD is limited.

**Objectives**

To describe the symptoms and lung function of Malawian adults up to 3-years following PTB-treatment completion, and to determine the evolution of PTLD over this period.

**Methods**

Adults successfully completing PTB treatment in Blantyre, Malawi were followed up for 3-years and assessed using questionnaires, post-bronchodilator spirometry, six-minute walk tests, high-resolution CT and chest x-ray. Predictors of lung function at 3-years were identified by mixed effects regression modelling.

**Measurement and Main Results**

We recruited 405 participants of whom 301 (mean(SD) age 35-years(10.2); 66.6% males; 60.4% HIV-positive) completed 3-years of follow up. At 3-years, 59/301 (19.6%) reported respiratory symptoms and 76/272 (27.9%) had abnormal spirometry. The proportions with low FVC and obstruction changed from 57/285 (20.0%) and 41/285 (14.4%) at TB treatment completion to 34/272 (12.5%) and 43/272 (15.8%) at 3-years. Absolute FEV₁ and FVC increased by mean 0.03L and 0.1L over this period, but a decline in FEV₁ of more than 0.1L was seen in 73/246 (29.6%) of participants. Better spirometry measures at 3-years were associated with higher BMI and HIV co-infection at TB-treatment completion.

**Conclusion**

On average, spirometry improves in the 3-years following TB-treatment completion, mostly in the first year. However, a third of PTB survivors experience ongoing respiratory symptoms and abnormal spirometry (with accelerated FEV₁ decline) at 3-years after TB treatment completion. Effective interventions are needed to improve the care of this group of patients.
At a Glance Commentary

Scientific Knowledge on the Subject
Following successful treatment for pulmonary TB, ongoing respiratory symptoms and abnormal lung function are well recognised. There is very limited understanding of how these change over time: to what degree should patients and physicians expect deterioration or even improvement?

What this Study Adds to the Field
We found that amongst adults in Malawi who had completed treatment for pulmonary TB, although one in five still had significant respiratory symptoms and more than one quarter had abnormal spirometry at 3-years after treatment completion, the majority improved with absolute FVC increasing by over 0.1L.
6.7 Background

In 2018, there were an estimated 10 million new cases of tuberculosis (TB) worldwide, of which a quarter occurred in sub-Saharan Africa (1). Over the last decade, TB survival has improved, in part due to higher treatment completion rates (currently 85%)(1). As a result, more people are living with long-term health consequences of having had TB disease, and received TB treatment (2). The importance of health and wellbeing post-TB was highlighted during a recent international symposium which identified major gaps in our understanding, and proposed a definition of post-TB lung disease (PTLD) as “evidence of chronic respiratory abnormality, with or without symptoms, attributable at least in part to previous pulmonary tuberculosis (PTB)” (3).

We have previously published a study describing the burden and natural history of PTLD in adults successfully completing PTB treatment in urban Malawi(3). This study showed that amongst 405 individuals (mean age 35-years; 77% microbiologically confirmed PTB; 61% HIV-positive), 61%, 34% and 44% had respiratory symptoms, abnormal spirometry and bronchiectasis at TB-treatment completion. In the year after treatment completion, the proportion of participants with respiratory symptoms and abnormal spirometry decreased, but a substantial minority (FVC decline 14% and FEV₁ decline 19.3%) of participants in fact experienced deteriorating lung function over time(3). These findings were limited by the short follow-up period of 1-year only. In this paper we describe findings of the extended follow-up this cohort for a further 2-years, to give a detailed description of the natural history of PTLD as defined by respiratory symptoms, spirometry and other health and wellbeing outcomes, in the period after TB treatment completion.

6.8 Methods

Study Design

We conducted a prospective longitudinal cohort study of adult PTB survivors, enrolled at completion of PTB treatment, and followed-up for 3-years. Details of the initial cohort design have been published elsewhere (3). Screening and recruitment were completed between February 2016 –April 2017, with the final 3-year follow up being completed in March 2020.
Setting

Participants were recruited from nine health centres in Blantyre, the second largest city in Malawi, with study visits conducted at Queen Elizabeth Central Hospital. Domiciliary visits were conducted throughout the study if required for logistical reasons.

Participants

Sequential adults were prospectively identified at pulmonary-TB treatment completion and were eligible for inclusion if they were 15 years or older, lived in Blantyre, and had been treated for a first episode of fully sensitive PTB with cure or completion as defined by the National Treatment Programme (3). Participants completing year one of study follow-up were invited to continue into a longer-term study with a further 2-years of follow-up. Participants gave written informed consent.

Procedures

Baseline data from TB-treatment completion and 1-year follow-up are available from the previously reported study.(3) These include HIV-status and CD4 counts, plain chest x-rays (CXR) taken at TB-treatment completion and 1-year, and non-contrast high-resolution computer tomography (HRCT) scans at TB-treatment completion.

Study visits were completed approximately 6-monthly for the 3-year period. For all visits, participants completed questionnaires administered by study staff, including demographics, socio-economic data, respiratory exposures, and the St George’s Respiratory Questionnaire (SGRQ). Health seeking and medical history were self-reported but confirmed using the participants’ health passport (a patient-held medical record). Six-minute walk tests and post bronchodilator ATS-standard spirometry (Easy One, NDD) were completed according to international standards (4, 5) by experienced staff with formal spirometry qualifications.

FEV₁ (forced expiratory volume) and FVC (forced vital capacity) were recorded as absolute volumes, and z-scores calculated using the Global Lung Initiative 2012 (GLI-2012) African reference ranges. Obstruction was defined as FEV₁/FVC below lower limits of normal (LLN) and Low FVC defined as FVC<LLN with FEV₁/FVC ≥LLN (6, 7). Obstructive severity was coded according to the Global Initiative for Chronic Obstruction Lung Disease (GOLD) guidelines (7, 8) (Supplement table 1E).
**Study Size**

The initial study sample size was based on a precision estimate for PTLD at TB-treatment completion, with a sample of 400 required to estimate PTLD prevalence with +/- 5% precision with 95% confidence, assuming a true population prevalence of between 10% and 50%. All participants in the initial study were invited to continue the extended follow-up.

**Statistical Methods**

Continuous variables are reported as mean (standard deviations, SD) or medians (interquartile range, IQR) and categorical data as frequency (%). We assessed for selection bias by comparison of those completing the study with those who were lost to follow up using $\chi^2$ and Student t-tests. Individuals completing follow-up were classified into three groups: “no change”, “improvement” or “decline” in clinical markers using pre-defined classifications of change over time (3). To account for individual variation in follow-up periods, continuous variables were normalised to the 3-year time point using the exact individual measurement interval (except in the longitudinal model of lung function). We tested the differences in the burden of disease using symptom scores, spirometry and six-minute walk test at TB-treatment completion and 3-years follow-up using McNemar’s and Wilcoxon Sign Rank test.

Associations between pre-specified predictors and FEV$_1$ and FVC over time were estimated using linear mixed-effects models, fitting a random effect for participant and adjusting for time from TB-treatment completion as a fixed effect. Independent variables were pre-determined based on past literature and clinical assumptions (Supplement figure 1). Radiological variables were selected based on the expert opinion of two pulmonologists, ensuring that the variables selected would highlight key pathologies. Given variable access to radiology in many low- and middle-income countries (LMICs), we produced 3 predictive models for each dependant variable (FEV$_1$ and FVC): 1) without radiology; 2) including CXR; 3) including HRCT but not CXR to minimise co-correlation effects. Associations between predictors and change in FEV$_1$ and FVC between TB-treatment completion and the 3-year study visit were estimated using linear regression models.
Data were analysed using Stata version 14.2 statistical software and R version 3.4. Statistical significance was tested at the 5% level.

Ethics

Ethical approval was obtained from the Liverpool School of Tropical Medicine (LSTM) (15.040RS and 17.089) and Malawi College of Medicine Research Ethics (COMREC) (P.10/15/1813 and P02/18/2349).

6.9 Results

405 participants were enrolled in the study at TB-treatment completion of whom 368 completed one-year follow up (3), and 319 participants were enrolled in the extended follow-up. Of the 49 participants who did not re-enrol, 37 (75.5%) were male and the mean age was 33.4 years (SD: 9.05). Reasons for not enrolling were: death (n=9); relocation (n=26); declined (n=3); medically unfit (n=1); unable to contact (n=10). At 3-years, follow-up data were available for 301 participants. The 18 participants who did not completed the study were due to death (n=4), relocation (n=7), withdrawal (n=1), loss to follow-up (n=2), and premature study closure due to COVID-19 (n=4). Amongst these participants, sex (n=12/18 male, 67%) and age (mean 34.5 years, SD 7.0) were not significantly different to the overall cohort (p=0.98 and p=0.88 respectively). The median time from TB-treatment completion to the final visit was 1,095 (1,080-1,130) days.
Figure 1: Participant Flow Diagram

Participant Characteristics

Of participants enrolled to extended 3-year follow-up (n=319), the median age at TB-treatment completion was 35.2 years (SD 10.2yrs), and 212 (66.5%) were male (Table 1). Amongst the 192 (60.4%) participants living with HIV, 179 (93.2%) were taking regular antiretroviral medication.

Socioeconomic deprivation was high; 191 people (91.2%) did not have piped water to their house, 128 (40.1%) were educated to primary school only or had no education and 236 (74.0%) had experienced dissaving since their TB diagnosis. Tobacco consumption was low: 92 (28.8%) reported having ever smoked, with a median of 3 pack-years consumption (IQR 1-6). Almost all participants used biomass as their main fuel (306, 95.9%).
Table 1: Participant characteristics at TB treatment completion for the 319 participants who enrolled to the extend follow up (years 2 &3 of the study).

<table>
<thead>
<tr>
<th>Characteristics n=319</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>35.2 (10.2)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>212 (66.5%)</td>
</tr>
<tr>
<td>Microbiological confirmed TB, n (%)</td>
<td>249 (78.1%)</td>
</tr>
<tr>
<td>HIV-positive, n (%)</td>
<td>192 (60.4%)</td>
</tr>
<tr>
<td>Taking ART (if HIV positive), n (%)</td>
<td>179 (93.2%)</td>
</tr>
<tr>
<td>CD 4 count, median cells/μl(IQR)</td>
<td>252 (154-407)</td>
</tr>
<tr>
<td>Self-reported respiratory condition prior to TB diagnosis*, n (%)</td>
<td>138 (43.3%)</td>
</tr>
<tr>
<td>Urban SES quintile (n=313), n (%)</td>
<td></td>
</tr>
<tr>
<td>- Poorest</td>
<td>20 (6.4%)</td>
</tr>
<tr>
<td>- 2nd poorest</td>
<td>77 (24.6%)</td>
</tr>
<tr>
<td>- Middle</td>
<td>79 (25.2%)</td>
</tr>
<tr>
<td>- 2nd most wealthy</td>
<td>93 (29.7%)</td>
</tr>
<tr>
<td>- Most wealthy</td>
<td>44 (14.1%)</td>
</tr>
<tr>
<td>Piped water into the dwelling, n (%)</td>
<td>28 (8.8 %)</td>
</tr>
<tr>
<td>Share a toilet with another household, n (%)</td>
<td>183 (57.3%)</td>
</tr>
<tr>
<td>Has electricity in the household, n (%)</td>
<td>170 (53.3%)</td>
</tr>
<tr>
<td>Maximum education ≤ primary school, n (%)</td>
<td>128 (40.1%)</td>
</tr>
<tr>
<td>Monthly household income, mean USD (SD)*</td>
<td>40 (60)</td>
</tr>
<tr>
<td>At least 1 child dropped out of school due to ill health of parent with TB, n (%)</td>
<td>56 (17.6%)</td>
</tr>
<tr>
<td>Household dissaving 1 year prior to TB treatment completion (borrowed money, loan, sold assets), n (%)</td>
<td>236 (74.0%)</td>
</tr>
<tr>
<td>Ever smoked tobacco, n (%)</td>
<td>92 (28.8%)</td>
</tr>
<tr>
<td>Tobacco smoking history, median pack-years (IQR)</td>
<td>3 (1-6)</td>
</tr>
<tr>
<td>Ever smoked Cannabis, n (%)</td>
<td>46 (15.9%)</td>
</tr>
<tr>
<td>Charcoal/wood (biomass) as main fuel, n (%)</td>
<td>306 (95.9%)</td>
</tr>
</tbody>
</table>

* Missing data: HIV-status n=1 - declined test at baseline; SES n=313 - unable to confirm housing type in 6 participants. House income n=225 due to participants not knowing their household income.

* the questioned asked was “Before you became unwell with TB, did a doctor / health care provider ever tell you that you had a problem with your lungs or breathing?

‡n=289, missing data for 30 participants

**Symptoms and other clinical features**

The prevalence of respiratory symptoms significantly reduced from treatment completion when 185/319 (60.0%) reported one or more respiratory symptoms (breathlessness, cough, regular sputum or wheeze in the preceding three months) compared to 59/301 (19.6%) of participants at 3-years, p<0.001 (Table 2). Using the SGRQ tool, the total score fell from median 9 (IQR 1-23) to 0 (IQR 0-1.44), over the same interval, p<0.001. Cough was the most frequently reported residual symptom at the 3-year visit, n=44/301 (14.6%).

Amongst those completing the extended follow-up, unscheduled health care seeking for a respiratory complaint (1 or more episode) was reported by 49/319 (15.3%) in their first year after completing TB treatment, falling to 27 (8.9%) participants in the last year of the study, p=0.03, of which the majority (17/27) reported only one episode.
Within this group, 11/319 participants were retreated for TB: eight were in the first year after treatment completion, one between the first and second year, and two between the second and third years after treatment completion.

**Spirometry**

The proportion of participants contributing ATS standard spirometry was 285/319 (89.3%) at TB-treatment completion, 292/319 (91.5%) at 1-year, 293/319 (91.8%) at 2-years and 272/301 (90.3%) at the final 3-year visit.

On average, spirometry parameters improved over time. Mean absolute FVC was 3.24L (SD 0.77) at 3-years post treatment completion, with a mean 0.10L (SD 0.29) improvement over the 3-year period (p<0.001) (Table 3). The mean FVC z-score significantly improved from -0.91 (1.21) to -0.64 (1.10) in this period, p<0.001. Mean absolute FEV1 did not significantly change from TB-treatment completion to the 3-year follow up (p=0.12), however FEV1 z-score improved from -1.07 (1.24) to 0.91 (1.16), p<0.001. Categorical interpretation of spirometry using both LLN and fixed ratio (GOLD) cut-offs was concordant with these findings: the proportion of participants with “low FVC” using these two definitions decreased from 57/285 (20.0%) to 33/271 (12.1%) and 70/285 (24.7%) to 40 (14.7%) respectively (p<0.001 for both).

There was no significant change in the number of participants classified as having obstructive pathology using LLN definitions (41/285(14.4%) at TB treatment completion vs. 43/272 (15.8%) at 3-year, p=0.39) (Figure 2). There was however an increase in obstructive patterns using fixed ratio interpretation (28/285 (9.8%) at TB-treatment completion vs. 36/272 (13.2%) at 3-years, p=0.04).

Overall, these categorical changes occurred mostly in the first 6 months, although transitioning from low FVC to normal or obstructive patterns is seen over the whole period (Figure 2).
Figure 2: a) FEV$_1$ z-score change (non-normalised individual intervals) b) FVC z-score change (non-normalised individual intervals) C) Sankey plot showing change of spirometry pattern (using GLI and LLN in those who completed ATS standard spirometry) between each visit from TB treatment completion to the final 3-year visit.
Table 2: Clinical parameters measured for the 3 years post-TB treatment completion

<table>
<thead>
<tr>
<th>Variable</th>
<th>TB Treatment completion</th>
<th>1 Year post TB treatment completion</th>
<th>2 years post TB treatment completion</th>
<th>3 years post TB treatment completion</th>
<th>P value comparing TB completion and Last visit $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Observations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen saturations, median % (IQR)</td>
<td>98 % (97-99%)</td>
<td>98% (97-98%)</td>
<td>98% (98-99%)</td>
<td>99% (98-100%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SpO2 &lt; 92%, n (%)</td>
<td>4 (1.25%)</td>
<td>2 (0.63%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.050</td>
</tr>
<tr>
<td>Respiratory Rate/minute, median (IQR)</td>
<td>19 (17-20)</td>
<td>20 (19-22)</td>
<td>20 (19-21)</td>
<td>20 (20-21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart Rate /minute, median (IQR)</td>
<td>78 (68-89)</td>
<td>77 (67-86)</td>
<td>71 (64-82)</td>
<td>73 (67-83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, median kg/m$^2$ (IQR)</td>
<td>20.5 (19-22.3)</td>
<td>21.2 (19.6-23.4)</td>
<td>21.3 (19.6-23.4)</td>
<td>21.3 (19.7-23.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Self-Reported Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breathlessness, n (%)</td>
<td>184 (57.7%)</td>
<td>122 (38.2%)</td>
<td>246 (77.1%)</td>
<td>281 (93.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cough, n (%)</td>
<td>207 (64.9%)</td>
<td>102 (32.0%)</td>
<td>265 (83.1%)</td>
<td>257 (85.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sputum, n (%)</td>
<td>237 (74.3%)</td>
<td>67 (21.0%)</td>
<td>277 (87.1%)</td>
<td>277 (92.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wheeze, n (%)</td>
<td>295 (92.5%)</td>
<td>10 (3.13%)</td>
<td>306 (95.9%)</td>
<td>295 (98.0%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Any respiratory symptom ≥ monthly, n (%)</td>
<td>185 (60.0%)</td>
<td>98 (30.72%)</td>
<td>94 (29.5%)</td>
<td>59 (19.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Impact of chest on activities, n (%)</td>
<td>156 (48.9%)</td>
<td>133 (41.7%)</td>
<td>257 (80.6%)</td>
<td>275 (91.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Impact of chest on work, n (%)</td>
<td>194 (60.8%)</td>
<td>112 (35.1%)</td>
<td>282 (88.4%)</td>
<td>288 (90.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Breathless at rest/during personal care, n (%)</td>
<td>1 (0.3%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.327</td>
</tr>
<tr>
<td>Walks slower than peers/stops for rest at own pace, n (%)</td>
<td>83 (26.2%)</td>
<td>53 (16.6%)</td>
<td>25 (7.8%)</td>
<td>16 (5.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Breathless on hills, n (%)</td>
<td>136 (42.9%)</td>
<td>70 (21.9%)</td>
<td>43 (13.5%)</td>
<td>38 (12.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Quality of life, median score (IQR)</td>
<td>9 (1-23)</td>
<td>0 (0-7)</td>
<td>11 (0-2.86)</td>
<td>0 (0-1.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SGRQ Total Score</td>
<td>10 (3-22)</td>
<td>3 (0-14)</td>
<td>4.4 (0-9.6)</td>
<td>0 (0-6.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SGRQ Activity Score</td>
<td>11 (0-35)</td>
<td>0 (0-6)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
SGRQ Impact Score | 6 (0-15) | 0 (0-4) | 0 (0-0) | 0 (0-0) | <0.001
---|---|---|---|---|---
**Care seeking** | | | | | |
Any self-reported acute respiratory OPD visit in the last 12 months*, n (%) | n/a | 49 (15.4%) | n/a | 27 (8.9%) | 0.027
Number of respiratory OPD visits in those that sought care*, n (%) | n/a | 40 (80.6%) | 6 (12.2%) | 3 (6.1%) | 0.007
Admission for illness in last 12 months*, n (%) | n/a | 21 (5.8%) | n/a | 13 (4.4%) | 0.178
Admissions for respiratory reason in last 12 months*, n (%) | n/a | 9 (2.8%) | n/a | 3 (0.9%) | 0.083
Retreated for TB in last 12 months*, n (%) | n/a | 8 (2.51%) | 1 (0.3%) | 2 (0.7%) | 0.058

* Data reported from the end of the first 12 months and end of 3 years of the study. Pairwise comparisons between TB treatment completion and 12-month data using McNemar’s test for categorical variables and Wilcoxon rank sum for continuous variables.

Table 3 Change in spirometry (completed to ATS standard) over the 3-years post TB-treatment completion.

<table>
<thead>
<tr>
<th>Variable</th>
<th>TB-treatment completion N=285</th>
<th>1-years post TB treatment completion N=292</th>
<th>2-years post TB treatment completion N=293</th>
<th>3-years post TB-treatment completion N=272</th>
<th>Mean change over 3-years (normalised to time)</th>
<th>P value comparing TB-treatment completion and 3-year visit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spirometry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC, mean L (SD)</td>
<td>3.17 (0.77)</td>
<td>3.30 (0.77)</td>
<td>3.33 (0.77)</td>
<td>3.24 (0.79)</td>
<td>0.10 (0.29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1, mean L (SD)</td>
<td>2.56 (0.68)</td>
<td>2.63 (0.67)</td>
<td>2.64 (0.66)</td>
<td>2.57 (0.66)</td>
<td>0.03 (0.24)</td>
<td>0.116</td>
</tr>
<tr>
<td>FVC Z-Score, mean (SD)</td>
<td>-0.91 (1.21)</td>
<td>-0.61 (1.11)</td>
<td>-0.55 (1.10)</td>
<td>-0.64 (1.10)</td>
<td>0.28 (0.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1 Z-score, mean (SD)</td>
<td>-1.07 (1.24)</td>
<td>-0.87 (1.18)</td>
<td>-0.81 (1.15)</td>
<td>-0.91 (1.16)</td>
<td>0.16 (0.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1/FVC ratio Z-score, mean (SD)</td>
<td>-0.38 (1.26)</td>
<td>-0.52 (1.30)</td>
<td>-0.56 (1.34)</td>
<td>-0.56 (1.30)</td>
<td>-0.19 (0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Spirometry pattern (GOLD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.041</td>
</tr>
<tr>
<td>Normal, n (%)</td>
<td>187 (65.6%)</td>
<td>211 (72.3%)</td>
<td>218 (74.4%)</td>
<td>196 (72.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild obstruction, n (%)</td>
<td>9 (3.16%)</td>
<td>5 (1.7%)</td>
<td>11 (3.8%)</td>
<td>8 (2.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate obstruction, n (%)</td>
<td>14 (4.91%)</td>
<td>25 (8.6%)</td>
<td>25 (8.5%)</td>
<td>25 (9.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe/v. severe obstruction, n (%)</td>
<td>5 (1.75%)</td>
<td>6 (2.1%)</td>
<td>4 (1.37%)</td>
<td>3 (1.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low FVC, n (%)</td>
<td>70 (24.6%)</td>
<td>45 (15.4%)</td>
<td>35 (12.0%)</td>
<td>40 (14.7%)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Spirometry pattern (LLN)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.394</td>
</tr>
<tr>
<td>Normal, n (%)</td>
<td>187 (65.6%)</td>
<td>200 (68.5%)</td>
<td>215 (73.4%)</td>
<td>196 (72.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstruction, n (%)</td>
<td>41 (14.4%)</td>
<td>53 (18.2%)</td>
<td>46 (16.4%)</td>
<td>43 (15.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low FVC, n (%)</td>
<td>57 (20.0%)</td>
<td>39 (13.4%)</td>
<td>30 (10.3%)</td>
<td>33 (12.1%)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reversible*</td>
<td>4 (1.25%)</td>
<td>7 (2.40%)</td>
<td>4 (1.37%)</td>
<td>1 (0.37%)</td>
<td></td>
<td>P=0.180</td>
</tr>
</tbody>
</table>

*ATS standard spirometry n=285/319 at TB-treatment completion=292/319 at 1-year visit n=293/319 at 2-year visit, n=272/301 at the 3-year last visit.

* Reversible spirometry with an FEV1 change of 12%.
**Change in clinical measures over time stratified by lung function at TB-treatment completion**

Despite improvements in symptoms and lung function at the group level, some individuals demonstrated worsening of FEV₁ and FVC of over 100ml from treatment completion to the 3-year visit (73/246, 29.75% and 52/246, 21.1% respectively). The distribution in lung function change is asymmetric, and non-normal on visual inspection as shown in Supplement Figure 2, providing some evidence for the existence of a proportion of patients with deteriorating spirometry. We therefore examined how participant outcomes at 3 years might be predicted by earlier spirometry.

When stratified by spirometry pattern at treatment completion, by 3-year follow-up, 68% (34/50) of those with “low FVC” had improved by over 0.1L (median change 0.31L, SD 0.24-0.50). Only 4/50 (8.0%) experienced further deterioration (Table 4). These participants also significantly improved with respect to respiratory quality of life (SGRQ decreased in 64.8%) and distance walked in the six-minute walk test (55.8% improved with median change of 80.2m, (IQR 46.3-94.5))

In those with a pattern of obstructive spirometry at TB treatment completion, 40.6% (15/37) had an improvement in FEV₁ of over 0.1L (median 0.17L, SD 0.13-0.29) at 3-years. Deterioration of over 0.1L in FEV₁ was noted in 10/37 (27.0%), with median change of -0.24L (-0.39--0.15). FVC also deteriorated in 29.7% (11/37) of this group, with a median deterioration of 0.16L (-0.18 -0.16)over the 3-year period.

Amongst those with normal spirometry at TB-treatment completion 47.8% (76/159) had a greater than 0.1L improvement in FVC (median change 0.23L, IQR 0.17-0.36) and 28.9% (46/159) of participants experienced an improvement in their FEV₁ (median change 0.21L, IQR 0.15-0.27)). However, 37/159 (23.3%) had decline in FVC of greater than 0.1L over the 3-year follow-up (median change -0.25L -(0.34 -0.16)) and 34.6% (55/159) had a decline in FEV₁ greater than 100ml with a median decline of 0.18L (-0.31- -0.12). Most other clinical outcomes continued to improve among this group with 46.3% experiencing an increase in SGRQ and 58.1% showing significant improvement in their 6-minute walk test compared to at TB treatment completion (median change 75.9m (50.8-103.9)) (table 4).
Table 4: Proportion of participants experiencing clinically relevant improvement, deterioration or change in health markers. Measure between TB-treatment completion visit and last visit at 3 years.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Classification of change</th>
<th>Improvement</th>
<th>No change</th>
<th>Deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>Change ≥1.46kg/m² *</td>
<td>15 (27.8%)</td>
<td>34 (63.0%)</td>
<td>5 (9.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.47 (1.9-4.9)</td>
<td>0.24 (-0.3-0.8)</td>
<td>-1.70 (-2.0--1.7)</td>
</tr>
<tr>
<td>SGRQ</td>
<td>Change ≥4 units **</td>
<td>36 (65.5%)</td>
<td>17 (30.9%)</td>
<td>2 (3.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-20.90 (-27.1--15.8)</td>
<td>0 (-0.98- 0)</td>
<td>20.12 (18.6-21.7)</td>
</tr>
<tr>
<td>6 minute walk test distance</td>
<td>Change ≥26m **</td>
<td>24 (55.8%)</td>
<td>11 (25.6%)</td>
<td>8 (18.60%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80.18 (46.3-94.5)</td>
<td>6.021 (-18.2-12.4)</td>
<td>-54.18 (-93.0--40.9)</td>
</tr>
<tr>
<td>6 minute walk test desaturation (spo2 less 92% at end of walk)</td>
<td>Change “yes” or “no”</td>
<td>2 (4.4%)</td>
<td>43 (95.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Presence of monthly symptoms</td>
<td>Change between present / absent monthly symptoms</td>
<td>29 (52.73%)</td>
<td>24 (43.6%)</td>
<td>2 (3.64%)</td>
</tr>
<tr>
<td>FEV1 (litres)$</td>
<td>Change ≥100ml **</td>
<td>27 (54.0%)</td>
<td>15 (30.0%)</td>
<td>8 (16.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.24 (0.17-0.39)</td>
<td>0 (-0.06- 0.02)</td>
<td>-0.16 (-0.18--0.16)</td>
</tr>
<tr>
<td>FVC (litres)$</td>
<td>Change ≥100ml **</td>
<td>34 (68.0%)</td>
<td>12 (24.0%)</td>
<td>4 (8.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.31 (0.24-0.50)</td>
<td>0.03 (-0.01-0.07)</td>
<td>0.32 (-0.34--0.26)</td>
</tr>
<tr>
<td>Unscheduled visit to healthcare for respiratory condition</td>
<td>Change ≥1 visit</td>
<td>12 (22.2%)</td>
<td>41 (75.9%)</td>
<td>1 (1.85%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1 (-1 -1)</td>
<td>0 (0)</td>
<td>2 (2-2)</td>
</tr>
</tbody>
</table>

Stratified to those who had obstruction at TB-treatment completion n =39

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Classification of change</th>
<th>Improvement</th>
<th>No change</th>
<th>Deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>Change ≥1.46kg/m²²</td>
<td>11 (28.2%)</td>
<td>24 (61.6%)</td>
<td>4 (10.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.78 (1.91-3.13)</td>
<td>0.30 (-0.05-1.00)</td>
<td>-1.55 (-2.23--1.50)</td>
</tr>
<tr>
<td>SGRQ</td>
<td>Change ≥4 units **</td>
<td>25 (65.8%)</td>
<td>12 (31.6%)</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-19.28 (-35.6--14.1)</td>
<td>-0.95 (-2.0-0.4)</td>
<td>12.73 (12.7-12.7)</td>
</tr>
<tr>
<td>6 minute walk test distance</td>
<td>Change ≥26m</td>
<td>12 (33.3%)</td>
<td>15 (41.7%)</td>
<td>9 (25.05%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>84.75 (55.74-122.15)</td>
<td>14.27-15.25)</td>
<td>-67.14 (-114.46--51.47)</td>
</tr>
<tr>
<td>6 minute walk test desaturation (spo2 less 92% at end of walk)</td>
<td>Change “yes” or “no”</td>
<td>5 (14.71%)</td>
<td>29 (85.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Presence of monthly symptoms</td>
<td>Change between present / absent monthly symptoms</td>
<td>21 (53.9%)</td>
<td>18 (46.2%)</td>
<td>0</td>
</tr>
<tr>
<td>FEV1 (litres)*</td>
<td>Change ≥100ml</td>
<td>15 (40.6%)</td>
<td>12 (32.4%)</td>
<td>10 (27.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.17 (0.13-0.29)</td>
<td>0.04 (-0.01-0.80)</td>
<td>-0.24 (-0.39--0.15)</td>
</tr>
<tr>
<td>FVC (litres)</td>
<td>Change ≥100ml</td>
<td>16 (43.2%)</td>
<td>10 (27.0%)</td>
<td>11 (29.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.20 (0.16-0.45)</td>
<td>-0.02 (-0.05-0.0)</td>
<td>-0.16 (-0.31--0.12)</td>
</tr>
<tr>
<td>Unscheduled visit to healthcare for respiratory condition</td>
<td>Change ≥1 visit</td>
<td>7 (18.4%)</td>
<td>30 (79.0%)</td>
<td>1 (2.6%)</td>
</tr>
</tbody>
</table>

Stratified by those who had normal TB-treatment completion spirometry n=176

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Classification of change</th>
<th>Improvement</th>
<th>No change</th>
<th>Deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>Change ≥1.46kg/m²²</td>
<td>68 (40.0%)</td>
<td>95 (55.9%)</td>
<td>7 (4.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.02 (2.86-4.59)</td>
<td>0.09 (-0.50-0.68)</td>
<td>-2.63 (-3.1--1.51)</td>
</tr>
<tr>
<td>SGRQ</td>
<td>Change ≥4 units **</td>
<td>86 (49.1%)</td>
<td>80 (45.7%)</td>
<td>9 (5.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-15.73 (-26.5--8.36)</td>
<td>0 (-1.8-0.0)</td>
<td>16.09 (10.2-19.61)</td>
</tr>
<tr>
<td>6 minute walk test distance</td>
<td>Change ≥26m</td>
<td>93 (58.1%)</td>
<td>39 (24.45)</td>
<td>28 (17.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75.90 (50.83-103.96)</td>
<td>3.91 (-0.06-12.02)</td>
<td>-53.88 (-82.51--40.99)</td>
</tr>
<tr>
<td>6 minute walk test desaturation (spo2 less 92% at end of walk)</td>
<td>Change “yes” or “no”</td>
<td>5 (3.1%)</td>
<td>152 (94.4%)</td>
<td>4 (2.5%)</td>
</tr>
</tbody>
</table>
Predictors at treatment completion of lung function over 3-years

Using linear mixed effects models adjusted for age, sex and time, and without any radiological variables, being HIV-positive was associated with a 0.19L greater mean FEV₁ over the 3-years (95% 0.06-0.31), as was having a higher BMI at TB treatment completion (0.09L/kg/m², 95%CI 0.03-0.16) (Table 5). The same associations were seen in models for FEV₁ z-scores (Supplement Table 3). When including radiological variables, the only significant predictors of FEV₁ other than age and sex were the percentage of abnormal parenchyma on HRCT which was significantly associated with a small decrease in FEV₁ (-0.001L per 1% (95%CI -0.001- -0.000), and percentage of normal lung on x-ray associated with a small increase in FEV₁ (0.014L, 95%CI 0.004-0.024). Longer duration of illness prior to TB diagnosis was associated with a lower mean FEV₁ Z-score (-0.16, 95% 0.29- -0.03) at 3-years, with this association found in all z-score models but not in absolute values.

In adjusted mixed effects models considering FVC as the outcome, positive associations were noted in those with HIV co-infection (0.177L, 95%CI 0.031-0.313) and higher BMI at TB-treatment completion (0.127L, 95%CI 0.056-0.199). The association with BMI remained statistically significant when including radiology in the model. Percentage of abnormal parenchyma on HRCT was a predictor of low FVC (-0.001 95%CI -0.002- -0.000), and similarly the percentage of normal parenchyma on CXR predicted increased FVC (0.0012 95%CI 0.001-0.024). FVC-z scores were higher in older participants and males. BMI was associated with a higher FVC z-score in the model without radiology only (0.24, 95%CI 0.11-0.36), the percentage of normal lung on X-ray was associated with a higher FVC z-score (0.03 95%CI 0.02-0.04).
0.01-0.05) whereas a higher ring and tramline score indicating radiological bronchiectasis was associated with lower FVC-z score (-0.14, 95%CI -0.27 - -0.01).

Factors associated with absolute change in FEV₁ between TB-treatment completion and the 3-year visit were age (-0.006L, 95%CI 0.009-0.003) and being HIV positive (0.083L 95% (0.017-0.150) at TB treatment completion. Older age (-0.007L, 95%CI0.010-0.004) and HIV positive status (0.104L 95%CI 0.030-0.180) were also significant predictors of change in FVC over the 3-years (Supplement Table 3). Ever-smokers had significant improvements in FVC in the models without HRCT included (0.103L, 95%CI 0.017-0.190). In models which included HRCT, FVC change was predicted by the total “tree in bud” score (0.013L, 95%CI 0.002-0.024) and the extent of consolidation (0.004L 95%CI 0.001-0.006) at TB-treatment completion. Percentage consolidation on x-ray (0.016 95% 0.004-0.0028) at TB treatment completion and pleural effusion on X-ray (0.180 95CI% 0.024-0.337) also predicted higher FVC change over the 3-years. The same patterns of predictors were seen in models describing the change FEV and FVC z-score over time (Supplement Table 4).

Table 5: Mixed effect regression model, investigating mean spirometry values in the 3-year follow up period after TB treatment completion

<table>
<thead>
<tr>
<th>Variable measured at TB treatment completion</th>
<th>Multivariate model no radiology</th>
<th>Multivariate model (HRCT)</th>
<th>Multivariate model (X-ray)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean absolute FEV1 (L) over the 3-year follow up period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since visits (days)</td>
<td>0.004 (-0.004-0.011)</td>
<td>0.004 (-0.004-0.011)</td>
<td>0.004 (-0.003-0.011)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.164 (-0.226 - -0.103)*</td>
<td>-0.145 (-0.203-0.087)*</td>
<td>-0.165 (-0.223--0.107)*</td>
</tr>
<tr>
<td>Gender male</td>
<td>0.859 (0.71-1.00)*</td>
<td>0.897 (0.760-1.034)*</td>
<td>0.880 (0.740-1.019)*</td>
</tr>
<tr>
<td>Microbiological diagnosed TB</td>
<td>0.044 (-0.106-0.194)</td>
<td>0.052 (-0.09-0.194)</td>
<td>0.034 (-0.108-0.175)</td>
</tr>
<tr>
<td>HIV positive status</td>
<td>0.185 (0.058-0.312)*</td>
<td>0.113 (-0.008-0.233)</td>
<td>0.119 (-0.003-0.242)</td>
</tr>
<tr>
<td>History of past respiratory illness</td>
<td>-0.103 (-0.221-0.016)</td>
<td>-0.100(-0.21--0.011)</td>
<td>-0.104 (-0.219-0.009)</td>
</tr>
<tr>
<td>Urban SES quintile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-2nd poorest</td>
<td>0.062 (-0.197-0.323)</td>
<td>0.084 (-0.163-0.333)</td>
<td>0.060 (0.479--0.185)</td>
</tr>
<tr>
<td>-Middle</td>
<td>0.038 (-0.227-0.303)</td>
<td>0.026 (-0.227-0.279)</td>
<td>0.048 (-0.202-0.298)</td>
</tr>
<tr>
<td>-2nd most wealthy</td>
<td>0.223 (-0.041-0.487)</td>
<td>0.179 (-0.074-0.431)</td>
<td>0.193 (-0.057-0.440)</td>
</tr>
<tr>
<td>-Most wealthy</td>
<td>0.294 (0.006-0.582)</td>
<td>0.252 (-0.022-0.527)</td>
<td>0.252 (-0.004-0.117)</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>-0.031 (-0.179-0.117)</td>
<td>0.049 (-0.093-0.191)</td>
<td>0.038 (-0.103-0.181)</td>
</tr>
<tr>
<td>BMI (Kg/m2)</td>
<td>0.093 (0.031-0.155)*</td>
<td>0.042 (-0.019-0.103)</td>
<td>0.056 (-0.004-0.117)</td>
</tr>
<tr>
<td>Unscheduled respiratory visits</td>
<td>-0.088 (-0.211-0.035)</td>
<td>-0.060 (-0.176-0.054)</td>
<td>-0.037 (-0.154-0.079)</td>
</tr>
<tr>
<td>Duration of illness pre-diagnosis</td>
<td>-0.058 (-0.120-0.003)</td>
<td>-0.038 (-0.098-0.021)</td>
<td>-0.044 (-0.104-0.015)</td>
</tr>
<tr>
<td>% abnormal parenchyma, excluding mosaicism (HRCT)</td>
<td>-0.001 (-0.002- -0.001)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 1 lobe destroyed (HRCT)</td>
<td>-0.046 (-0.253-0.160)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total lung bronchiectasis dilatation severity score (HRCT)</td>
<td>-0.023 (9-0.050-0.003)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total tree in bud severity score (HRCT)</td>
<td>-0.003 (-0.021-0.014)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total lung extent/number score (HRCT)</td>
<td>-0.003 (-0.033-0.028)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In this cohort of adults successfully completing PTB treatment, we described an initial high burden of lung disease in which 60% still reported one or more respiratory symptoms and 34.4% had abnormal spirometry (3). In this paper, we show that 3-years after treatment completion most people had significantly improved symptoms (19.6% experiencing symptoms). However, 27.9% had abnormal spirometry, mostly obstruction (15.4%). When looking at patterns of change over time, the majority of the cohort experienced no change

| Total consolidation score, across whole lung (HRCT) | -0.001 (-0.005-0.003) |
| % normal, across whole lung (X-ray) | 0.014 (0.004-0.024)* |
| % consolidation, across whole lung (X-ray) | -0.009 (-0.03-0.011) |
| Total lung ring & tramline score (X-ray) | -0.046 (-0.11-0.021) |
| Pleural effusion (X-ray) | -0.086 (-0.366-0.195) |

| Total consolidation score, across whole lung (HRCT) | -0.001 (-0.005-0.003) |
| % normal, across whole lung (X-ray) | 0.014 (0.004-0.024)* |
| % consolidation, across whole lung (X-ray) | -0.009 (-0.03-0.011) |
| Total lung ring & tramline score (X-ray) | -0.046 (-0.11-0.021) |
| Pleural effusion (X-ray) | -0.086 (-0.366-0.195) |

**Mean absolute FVC (L) over 3-year follow up period**

| Time since visits (days) | 0.024 (0.015-0.033)* | 0.024 (0.015-0.033)* | 0.024 (0.015-0.032)* |
| Age (years) | -0.087 (-0.157-0.016)* | -0.073 (-0.142-0.005)* | -0.090 (-0.158-0.023)* |
| Gender male | 1.033 (0.867-1.200)* | 1.067 (0.904-1.231)* | 1.064 (0.903-1.226)* |
| Microbiological diagnosed TB | 0.074 (-0.097-0.246) | 0.077 (-0.091-0.245) | 0.064 (-0.100-0.229) |
| HIV positive status | 0.177 (0.031-0.323)* | 0.113 (-0.031-0.257) | 0.109 (-0.033-0.251) |
| History of past respiratory illness | -0.129 (-0.266-0.007) | -0.124 (-0.256-0.008) | -0.120 (-0.253-0.012) |
| Urban SES quintile | | | |
| -2nd poorest | 0.075 (-0.224-0.374) | 0.083 (-0.212-0.377) | 0.074 (-0.211-0.359) |
| -2nd most wealthy | 0.122 (-0.208-0.452) | 0.063 (-0.238-0.363) | 0.070 (-0.221-0.361) |
| -Most wealthy | 0.122 (-0.207-0.452) | 0.079 (-0.248-0.406) | 0.070 (-0.25-0.386) |
| Ever smoked | 0.081 (-0.089-0.250) | 0.160 (-0.010-0.329) | 0.152 (-0.0121-0.317) |
| BMI (K/m2) | 0.127 (0.056-0.199)* | 0.0842 (0.011-0.157)* | 0.090 (0.020-0.161)* |
| Unscheduled respiratory visits | -0.105 (-0.246-0.004) | -0.079 (-0.217-0.059) | -0.051 (-0.187-0.084) |
| Duration of illness pre-diagnosis | -0.041 (-0.113-0.029) | -0.027 (-0.098-0.005) | -0.029 (-0.098-0.040) |
| % abnormal parenchyma, excluding mosaicism (HRCT) | -0.001 (-0.002-0.000)* |
| At least 1 lobe destroyed (HRCT) | -0.101 (-0.347-0.146) |
| Total lung bronchiectasis dilatation severity score (HRCT) | -0.024 (-0.056-0.007) |
| Total tree in bud severity score (HRCT) | 0.002 (-0.019-0.023) |
| Total lung cavity extent score (0-18) (HRCT) | -0.012 (-0.049-0.002) |
| Total consolidation score, across whole lung (HRCT) | -0.013 (-0.049-0.024) |
| % normal, across whole lung (X-ray) | 0.012 (0.001-0.024)* |
| % consolidation, across whole lung (X-ray) | -0.001 (-0.034-0.013) |
| Total lung ring & tramline score (X-ray) | -0.059 (-0.138-0.019) |
| Pleural effusion (X-ray) | -0.286 (-0.611-0.040) |

* statistically significant at p<0.05 level

6.10 Discussion

In this cohort of adults successfully completing PTB treatment, we described an initial high burden of lung disease in which 60% still reported one or more respiratory symptoms and 34.4% had abnormal spirometry (3). In this paper, we show that 3-years after treatment completion most people had significantly improved symptoms (19.6% experiencing symptoms). However, 27.9% had abnormal spirometry, mostly obstruction (15.4%). When looking at patterns of change over time, the majority of the cohort experienced no change.
or an improvement in FEV$_1$ and FVC, however a proportion had substantive (over 0.1L) decline in spirometry (FEV$_1$ 29.7% and FVC 21.1%), which was not limited to those that had abnormal spirometry at treatment completion.

Lung function at 3-years was better in those who had higher BMI and those who were HIV positive at treatment completion. The extent of tree-in-bud pathology on HRCT and parenchymal change or pleural effusion on CXR predicted improvement in lung function over 3-years, whilst more extensive ring and tramline change at treatment completion was associated with lower FVC z-score at 3-years.

The high burden of PTB lung disease reported here is consistent with other literature and replicated the findings from our original cohort (3, 11-13). Symptoms were more common than reports from the wider population in Blantyre (19.6% v 11.8%), as was obstructive lung function abnormality (15.4% v 4.2%) (14). While the effect of PTB on lung function is well documented, reports on how this changes over time are sparse. In spontaneously healed pulmonary-TB patients in South Korea, FEV$_1$ decline overtime has been demonstrated to exceed that of uninfected individuals (15). Amongst South African miners, an increasing number of prior PTB episodes was associated with a greater deficit in both FEV$_1$ and FVC compared to miners without a TB history (15, 16). A separate study of HIV-positive TB patients in South Africa, estimated a 35ml excess FEV$_1$ loss per year and a 57ml excess FVC loss (17).

In adulthood, an average decline of 30ml a year in FEV$_1$ is normal(9). In this cohort recovering from PTB, the majority experienced an improvement in FEV$_1$ of 30ml in 3-years (or 10ml/year). However 29.7% of all participants experienced a decline over 100ml over the 3-years (or 33ml/year) and amongst this group the median decline in FEV$_1$ was 180ml (or 60ml/year), which is similar to those with tobacco-related COPD (18, 19). The primary driver of this decline is unclear from the models we developed, however possible drivers may include chronic colonisation with other pathogens, nutritional status, HIV co-infection or environmental factors such as exposure to biomass.

We saw the burden of low FVC decrease over 3-year follow-up, and the burden of obstruction non-statically significantly increased. In our participants, this change in pattern
appears to represent significant improvement in FVC compared with FEV₁, which may reflect structural recovery rather than disease progression. Other studies have reported a change to an obstructive pattern from a restrictive pattern, with suggestions this maybe due to progression of small airways pathology during the healing process (20).

Our finding that those with HIV positive participants had higher FEV₁ and FVC at 3-years of follow-up is consistent with our observations at TB treatment completion (3). Although the majority of participants were on ART, many were severely immunosuppressed even by the point of PTB treatment completion, which may suggest that impaired immune response to mycobacteria during the acute PTB phase is associated with less lung destruction (21). However as an overall group there was still a high burden of PTLD seen amongst HIV-infected participants, which may be associated with immune reconstitution within the HIV co-infected participants included in this study, many of whom initiated ART close to treatment for PTB (3, 22).

Our findings support the finding that a proportion of TB survivors have persistent symptoms and poor lung function at 3-years TB-treatment completion. Negative HIV status, low BMI, and extensive lung parenchymal change appears to predict lung function decline, but abnormal spirometry at the end of TB-treatment does not. Interestingly chest x-ray at treatment completion appears to be a better predictor of mean 3-year lung function than HRCT. In LMIC it may be that a simple score of “normal” lung on chest x-ray is both helpful and more accessible than HRCT.

To the best of our knowledge we are the first group to have recorded all of spirometry, symptoms and radiological findings prospectively over a 3-year period post PTB-treatment completion. While our study is limited by the lack of a control group, previous cross-sectional research has shown the effect of TB on lung function, and our focus here was on within-individual changes over time. Limitations also include recruitment from a single site which may limit generalisability, and recall bias related to prior illness and recent healthcare usage. There may have been selection bias at initial enrolment, or during follow-up, with those with poor or declining health less likely to attend study visits and therefore relatively under-represented in our study. However, strengths of this study include prospective
recruitment, and had high rates of retention (76% of participants for 3-years) for a study of this duration and type.

In summary, our findings show that whilst the majority of post pulmonary-TB patients experienced improved symptoms and lung function, others continued to have a substantial burden of symptoms and lung function abnormalities even three years after TB treatment completion. This population is likely to become larger as TB survival improves (23). Whilst there is understandably a focus on treatment of active TB disease, patients who have suboptimal recovery have limited access to care and few treatment options (2). Formal guidance on individual patient management of health and wellbeing post-TB are lacking, but would be welcomed by clinicians (24). Guideline development should be underpinned by research to determine what interventions would be clinically- and cost-effective (25). The potential for improving the health, psychosocial and economic status amongst this group of overlooked patients is huge. However, interventions at the health system level are unlikely to be prioritised without a deeper understanding of the drivers of residual symptoms and lung function decline, and their economic ill-effects. Concerted efforts should test the role of pulmonary rehabilitation, the potential for enhanced and early identification of modifiable chronic lung disease, and their acceptability and uptake in those most affected: TB survivors.
6.11 References


Chapter 7: Discussion

In this thesis I hypothesised an increased burden of respiratory disease, as measured by symptoms and spirometry, amongst those living in disadvantaged situations and those exposed to possible high-risk activities or disease (heroin smoke, biomass fuel and TB). This chapter presents a summary of the main findings from the five papers exploring this hypothesis. It provides suggestions for future research and possible policy and health system implications.

7.1 Summary of Main Findings

7.1.1 Heroin Smokers with COPD in Liverpool

In Chapter 2, I reported that Heroin smokers with COPD appear to be at high risk of accelerated lung disease, with an annual average FEV₁ decline of 90ml (SD 190, p<0.001). Although showing causality was difficult due to the complex smoking habits of this population, this decline is more than is typically observed in tobacco-only smokers with COPD (1, 2). Alongside this considerable burden of worsening spirometry, participants experienced worsening symptoms, and over 10% of the population had emergency admission for respiratory conditions over a 12-month period. It was clearly expressed from the participants themselves (Chapter 3) that their respiratory condition had an impact on their activities of daily living and there was significant stigma attached to having a respiratory problem that was attributed to illicit drug use. Accessing care including guidance on the correct use of inhalers was a huge challenge. Although we did not interview healthcare workers, the erratic behaviour and inappropriate medicine use is potentially a challenge to health care professionals and the wider health system in Liverpool.

7.1.2 Lung Health in Malawi

The systematic review (Chapter 5) reported both a high burden of chronic respiratory disease in Malawi but also highlighted the heterogeneity of data, particularly surrounding the use of spirometric reference ranges, meaning that country-specific estimates are very difficult to undertake with great accuracy. This highlighted the need for further robust research into chronic non-communicable respiratory disease in Malawi. The high burden of abnormal spirometry reported in the literature (Chapter 5) was also the main finding of the cross-sectional study in Chikwawa (Chapter 4). Perhaps surprisingly, and despite finding very
high levels of air pollution, there was very little evidence that abnormal spirometry or having chronic respiratory symptoms was associated with measured air quality. This population do however appear to be at high-risk of abnormal spirometry, the reasons for which have yet to be fully understood but are discussed later in this chapter. Post-Tuberculosis Lung Disease (PTLD) was one possible reason for abnormal spirometry in Malawi. The longitudinal study presented in Chapter 6 highlighted that while the majority of a post-PTB cohort had significant improvement in lung function over the first 12 months, there were a group of patients who still experienced chronic respiratory symptoms (19.6%) and had abnormal spirometry (27.9%) 3-years after completing their TB treatment. It is therefore possible that PTLD is one of the factors leading to the high rate of abnormal spirometry seen in the community in Malawi.

7.1.3 Summary of Lung Disease in These High-Risk Populations

The overarching theme of this thesis has been chronic respiratory disease in high-risk populations. All the populations that took part in this thesis are potentially disadvantaged because of poverty, their medical history, living conditions, or the substances they smoke. In all three of the populations it was hypothesised that their circumstances may result in a high burden of respiratory disease. In the case of heroin smokers with COPD, an accelerated decline in FEV₁ was reported. In the high-risk rural population with biomass exposure, abnormal spirometry was reported in over 40% of the population, although not attributable to the biomass itself. In post-PTB patients, there was a sub-group of the population who still had abnormal spirometry three years after TB treatment completion. In all these populations there are potential policy and health system implications as well as a clear need for further research involving these disadvantaged groups.

7.2 Implications for Health Systems and Policy in Liverpool

Liverpool is a city with extremely high levels of heroin smokers (3). The evidence presented in this thesis and from elsewhere with Liverpool shows that COPD is a significant problem among this population and puts a burden on both the primary care service and acute hospital admissions (3-6). Public health officials, NGOs and researchers have all aimed to reduce the significant harm heroin can cause. In the past, drugs charities have provided foil as a harm-reduction method to prevent both accidental overdose and blood-borne disease
While it is beyond the scope of this thesis to determine the overall risk of smoking compared to injecting heroin, it is clear from the evidence presented that the effects of smoking heroin on the risk of COPD need to be considered when planning harm-reduction policies. These data have already been presented and discussed at education sessions with attendees from Addaction and other local service providers, drug charities, the British Thoracic Society winter meeting, and the Drug Related Deaths North West meetings (3). Harm-reduction in heroin users is complex, but each component should be understood in terms of its own risk:benefit. Such analysis is informed by this work presented here.

Alongside managing the risk of developing COPD, the medical management of the current population of heroin smokers already diagnosed with COPD in Liverpool is vital. Although we saw a high lost to follow up rate over the 24-month period following this cohort, we do show that it was feasible to provide a spirometry and respiratory assessment service at opiates substitution therapy (OST) clinics. A possible solution that is being explored is providing a ‘one-stop shop’ at the OST clinics, which has been shown to work in neighbouring Knowsley (8) and has worked well for the treatment of hepatitis C in this population in Liverpool. A tailored respiratory programme could potentially be provided by healthcare professionals who can assess spirometry and provide appropriate medication (for example considering other options before prescribing a metered dose inhaler often used as drugs paraphernalia), monitoring and education. It was clear from qualitative interviews (Chapter 3) that heroin users have significant challenges in accessing respiratory services. This is likely to contribute to sub-optimal use of medications: noting the fact that recording a patient has picked up medication may not be a sufficient measure of treatment adherence. The papers presented in this thesis have contributed to proposals put forward by the local commissioning group that would trial a ‘one stop’ respiratory care service at the OST ‘anchor points’.

7.3 Future Research in Heroin Smokers

The papers presented in Chapter 2 and 3 provide an insight into the respiratory disease seen in relatively ‘stable’ heroin smokers already diagnosed with COPD, in order to obtain a more detailed picture of the natural history of respiratory disease seen in heroin smokers. In general, an unselected cohort study of heroin smokers would answer the question of whether this lung function decline is universal, or if there are specific additional risk factors
or behaviours which determine it. Research focused upon those deemed ‘non-stable (for example injecting as well as smoking heroin)’ heroin users would also give a wider picture of the problem amongst heroin users more generally, for example those in prisons and among the homeless population. Although it would be ideal to test the hypotheses in a population who exclusively smoke heroin, in this population this is likely to be unrealistic option due to the complex smoking habits displayed by most individuals. Therefore, following an age and socio-economic- matched cohort of just tobacco smokers and non-smoking control group is likely to be the best option available. The chaotic lifestyles of heroin smokers make research in this group more challenging than in other populations. Ensuring that research is conducted in a manner that fits in with their routine of picking up OST and alongside keyworkers visits is likely to be vital to obtaining the highest quality data possible. As with most health systems worldwide, there are limited resources within the UK. Commissioners and health service managers require data on the clinical outcomes and cost effectiveness of providing services that are tailored to the needs of heroin smokers. One possible option would be conducting an interventional trial assessing both the clinical effectiveness and costs/benefits of running respiratory services within OST clinics.

7.4 Implications for Health Systems and Policy in Malawi

It is clear from all three papers presented from Malawi (Chapters 4, 5 and 6) that non-communicable respiratory disease in Malawi is a potential burden on the healthcare system. Currently in Malawi most resources are aimed at childhood disease and communicable adult diseases such HIV and tuberculosis. However it is becoming well recognised that there is a growing burden of non-communicable disease in Africa, and this is likely to put an increased strain on the health system in years to come (9). There is currently a drive for universal healthcare in Malawi. In the long term incorporating the early detection and management of chronic disease into the health system will be required (10). Further research is needed into the causes of abnormal spirometry and increased symptoms in the community (discussed further in the next section) in order to allow for decision making at policy level in a world of competing priorities. Chapter 6 described one possible cause of abnormal spirometry in adult in Malawi, PTLD, highlighting a subgroup of the population in whom PTB symptoms did not end at treatment completion. Based on TB incidence, the potential to improve health and wellbeing in this group is vast. However, intervention models such as
providing a follow up service for these patients, would need to be explored further within the context of the resources available and the potential treatment options. Currently, guidance on individual patient management of health and wellbeing in those with PTLD are lacking, but would be welcomed by clinicians (11). However, guideline development should be underpinned by research to determine possible treatments and management strategies that are both cost effective, beneficial to the patients and practical in the environment they are used in.

7.5 Future Research in Chronic Disease in Malawi

The cause of the high level of abnormal spirometry seen in Malawi – particularly low FVC – is not yet known. A key factor in concluding if a person has ‘abnormal’ spirometry is the reference ranges applied to determine predicted values. As highlighted in the systematic review (Chapter 5) the lack of standard spirometric reference ranges is problematic when comparing literature. There is still no academic consensus about the appropriate reference range to use. NHANES which is used in the BOLD studies is based on African-American measurement of ‘normal’, and in BOLD studies is often reported alongside the local ranges, which are non-validated internationally as they are based purely on healthy non-smokers living in Blantyre, Malawi. With an increase in lung health research in Africa, the question of reference ranges requires addressing, asking the question: is it acceptable to assume that on average Africans have smaller lungs, and therefore reference ranges should reflect this? Or in fact is the apparent low FVC seen in African populations related to circumstances of poverty or ill-health, or wider environmental determinants. In order to achieve comparable high-quality research, a consensus among key researchers in lung health in Africa needs to be reached and if local references are used, they are robustly validated.

Since the publication of the cross-sectional study in Chikwawa two further studies have been published linked to this cohort. The first focused on children in the same households as the adult study (Chapter 4) which reported a high burden of disease among children, suggesting that early nutrition or in utero causes may be linked to the abnormal spirometry seen in adults (12). There is a lack of clinical data on lung function in children in sub-Saharan Africa. It possible their lung function ‘tracks low’ throughout their life leading to lower volumes at peak lung maturation but the clinical and environmental determinants of this are not yet known (12-14). A longitudinal study of the same cohort of adults showed an
average decline in FEV\(_1\) of approximately 30ml annually which is not abnormally high compared to other healthy populations globally. However, a sub-optimal peak in lung growth would mean that, given the same absolute rate of decline, thresholds for respiratory compromise would be reached earlier in life (12, 15). This suggests that further research into the determinates of abnormal spirometry seen in Malawian adults should focus on infant lung function, and childhood or maternal care.

Currently the literature surrounding chronic respiratory disease in Malawi is mostly observational in nature. In time this should extend to finding cost effective solutions that will help those in Malawi suffering from both PTLD and other chronic lung disease. For PTLD the drivers of the abnormal spirometry, decline in lung function or persistent symptoms are still not fully clear. Ensuring adequate nutrition to achieve normal BMI and earlier diagnosis of PTB may improve spirometric outcomes. Unwell PTLD patients presented with a mix of spirometric abnormality and clinical symptoms, so it is likely there is more than one driver of PTLD. However potential areas of further investigation include probing further into the pathogens present at PTB diagnosis and after treatment completion, for example Aspergillus and also symptoms-based interventions to improve individuals’ functional status. These interventions may include antibiotic trials or other low cost and situation-appropriate treatments such as airway clearance and pulmonary rehabilitation. There are currently ongoing studies both in Uganda and Malawi that will contribute to the available evidence base for these low-cost solutions. Alongside this, qualitative research that lets us further understand the ‘voice’ of those with PTLD is vital, and at the heart of further research there needs to be a commitment to ensuring TB survivors are part of the design and development of new interventions.

7.6 Similarities in These Populations

Throughout this thesis I have presented data from three populations from different settings, and yet many of challenges they present with are similar. All three populations live with a high burden of respiratory disease and often due to poverty, location or circumstances may struggle to access the optimal healthcare for their needs. Although the health systems in Liverpool and Malawi are different, both countries are striving for the international goal of Universal Health Coverage for all. Meeting the needs of these often disadvantaged populations is one of the challenges facing policy makers in both settings, but is key to
reaching the Sustainable Development Goal 3: ‘ensuring healthy lives and promote well-being for at all ages’ (16).

7.7 Conclusion

In conclusion I have presented research relating to three high-risk, disadvantaged groups of patients from different parts of the world, all of whom for different reasons have a high burden of respiratory disease both symptomatically and based on spirometry. All three populations could be adversely affected by their lung health and have healthcare needs which the current configuration of healthcare services struggles to meet. Managing lung health in these populations requires careful planning, taking into account the population, resources and setting, with providers of healthcare, public health teams, researchers and affected individuals working together to establish the optimal management plans both for the wider health system and those who are living with these conditions.
7.8 References


Appendix for Chapter Two

Section 1: PDF of Paper
Screening Heroin Smokers Attending Community Drug Clinics for Change in Lung Function
A Cohort Study

Rebecca Nightingale, MSc; Kevin Mortimer, MD, PhD; Emanuele Giorgi, PhD; Paul P. Walker, MD; Marie Stolbrink, MD; Tara Byrne, BSc; Kerry Marwood, NVQ; Sally Morrison-Grifths, MD; Susan Renwick, MPH; Jamie Rylance, MD, PhD; and Hassan Burhan, MD

BACKGROUND: Heroin smokers have high rates of COPD, respiratory morbidity, hospital admission, and mortality. We assessed the natural history of symptoms and lung function in this population over time.

METHODS: A cohort of heroin smokers with COPD was followed for 18 to 24 months. At baseline and follow-up, respiratory symptoms were measured by the Medical Research Council Dyspnea Scale (MRC) and the COPD Assessment Tool (CAT), and postbronchodilator spirometry was performed. Frequency of health-care-seeking episodes was extracted from routine health records. Parametric, nonparametric, and linear regression models were used to analyze the change in symptoms and lung function over time.

RESULTS: Of 372 participants originally recruited, 161 were assessed at follow-up (mean age, 51.0 ± 5.3 years; 74 women [46%]) and 106 participants completed postbronchodilator spirometry. All participants were current or previous heroin smokers, and 122 (75.8%) had smoked crack. Symptoms increased over time (MRC score increased by 0.48 points per year, \( P < .001 \); CAT score increased by 1.60 points per year, \( P < .001 \)). FEV\(_1\) declined annually by 90 ± 190 mL (\( P < .001 \)). This deterioration was not associated with change in tobacco or heroin smoking status or use of inhaled medications.

CONCLUSIONS: Heroin smokers experience a high and increasing burden of chronic respiratory symptoms and a decline in FEV\(_1\) that exceeds the normal age-related decline observed among tobacco smokers with COPD and healthy nonsmokers. Targeted COPD diagnostic and treatment services hosted within opiate substitution services could benefit this vulnerable, relatively inaccessible, and underserved group of people. CHEST 2020; 157(3):558-565

KEY WORDS: COPD; heroin; opiate; spirometry

ABBREVIATIONS: ACO = asthma-COPD overlap; ATS = American Thoracic Society; CAT = COPD Assessment Tool; GOLD = Global Initiative for Chronic Obstructive Lung Disease; MRC = Medical Research Council Dyspnea Scale; OST = opiate substitution therapy

AFFILIATIONS: From the Liverpool School of Tropical Medicine (Ms Nightingale; and Drs Mortimer and Rylance), Liverpool, England; CHICAS (Dr Giorgi), Lancaster University, England; the University Hospital Aintree (Drs Walker and Stolbrink), Liverpool, England; Addaction (Mss Byrne and Marwood; and Dr Morrison-Grifths), Liverpool, England; the Liverpool Clinical Commissioning Group (Ms Renwick), Liverpool, England; the Malawi-Liverpool-Wellcome Trust Clinical Research Programme (Dr Rylance), Blantyre, Malawi;
Illicit drug use is common, with 8.5% of adults in England and Wales having reported taking an illicit drug in 2016 and 2017. Over the last 30 years, smoking rather than injecting heroin has become more common. In recent years, smoking heroin rather than injecting has been used as a possible method of harm reduction.

Although the effects of illicit drug use are well documented, there is limited evidence about the chronic effects of inhaled illicit drug use on the respiratory system. Multiple case reports highlight acute asthma attacks in heroin users, and observational studies report a high prevalence of respiratory disease in heroin users admitted to acute hospitals. Severe early onset emphysema associated with premature mortality has been reported among heroin users. However, large-scale diagnostic studies in this hard-to-reach population are lacking. Chronic respiratory symptoms are common in people inhaling heroin; however, access to formal diagnosis including lung function measurement is limited.

We recently reported postbronchodilator spirometry in 703 heroin smokers attending for opiate substitution therapy (OST) at community drug service clinics in Liverpool, England; 50% of heroin smokers had either COPD or asthma-COPD overlap (ACO) despite a mean age of 47 years. This was associated with extensive respiratory symptoms, which given the known high rates of COPD hospitalization and a continuing trend toward inhalation as the mode of drug use, is likely to put increased burden on health systems. In light of this, screening and treatment programs for heroin smokers could be a viable method for identifying and treating disease in this relatively inaccessible patient group.

We performed a longitudinal cohort study of heroin smokers attending community drug services and who were recruited as an original cohort of 703 heroin smokers described in terms of baseline characteristics in our previous paper. The aim was to ascertain their change in health status, respiratory symptoms, and lung function over an 18- to 24-month period.

Methods

Setting

The study was performed in 31 community drug service clinics in Liverpool. Clinics are run by Addaction, a large independent charity commissioned by the local city council public health department. A keyworker who knew the client and who coordinated their OST worked with the study team in each clinic.

Participants

Participants were invited to take part if they had previously completed spirometry in the baseline screening project that took place between December 2015 and June 2016, were > 18 years of age, and were still fully enrolled in Addaction’s service. All participants were current or previous smokers of heroin and were currently or recently treated with methadone or buprenorphine. Participants were given the study information prior to being booked for their regular appointment and were offered a study visit at their usual clinic. People missing their usual appointment were offered another at a central venue. Written informed consent was obtained from all participants.

Variables and Data Source

Baseline data collection has been previously described. In brief, participants completed a questionnaire detailing demographic data, and self-reported tobacco and illicit drug use. Oxygen saturations were measured, and pre- and postbronchodilator spirometry was completed. At follow-up, participants completed a questionnaire which evaluated self-reporting medication prescriptions, health-care access, and ongoing tobacco and illicit drug use. The index of multiple deprivation, which is an official geographic measure of relative deprivation in England, was used as a proxy of social-economic status. Participants also completed the COPD Assessment Tool (CAT) and the Medical Research Council Dyspnea Scale (MRC), and consented to allow review of 2 years of medical records for respiratory-related diagnosis and prescriptions from primary care pharmacy records (EMIS), and hospital records where applicable.

Oxygen saturations were measured, and pre- and postbronchodilator spirometry was performed on all participants who consented and did not have medical contraindications. Spirometry was performed by trained clinical staff and completed according to American Thoracic Society (ATS) guidelines. All traces were double-reviewed for quality and grading by an experienced respiratory physician. As with the baseline survey, participants were asked not to take a short-acting bronchodilator within 8 h of visit or a long-acting bronchodilator within 24 h. If they had taken a short-acting inhaler, only postbronchodilator spirometry was recorded.

Subjects were categorized based on original screening. A diagnosis of asthma was given if airflow obstruction (FEV1/FVC ratio < 0.7) was fully reversible to inhaled salbutamol (ie, either FEV1/FVC normalized or FEV1 increased by ≥ 400 mL), or if spirometry was normal but the participant had a prior physician diagnosis of...
asthma. Participants with nonreversible airflow obstruction were characterized as COPD unless they had a prior physician diagnosis of asthma, in which case their condition was labeled as ACO. We report the lung function change of participants who had been diagnosed with COPD or ACO at baseline; participants with an asthma diagnosis were excluded.\textsuperscript{17}

All spirometry data were reported using the European Coal and Steel Community\textsuperscript{24} reference ranges for consistency with prior work. Abnormal spirometry was defined using the Global Initiative for Chronic Obstructive Lung Disease (GOLD).\textsuperscript{25} Change in lung function was based on postbronchodilator FEV\textsubscript{1}.

**Sample Size**

We aimed to follow-up as many of the participants with COPD or ACO from baseline as possible.

**Statistical Analysis**

Univariate analysis was carried out using descriptive statistics to explore the characteristics of the study populations. Paired t tests and Wilcoxon sign rank tests (with bootstrapping to estimate the CI of the difference) were used to assess change between the two time points. Time was used as a continuous variable to account for variation between follow-up dates and to calculate an annualized change. A linear regression model was used to estimate the effect of potential factors (change in inhaled illicit drug use, change in tobacco smoking, and change in inhaler use) on changes in FEV\textsubscript{1} over time. Variables were selected for the model a priori based on clinical data which might have varied over the course of follow-up within an individual, specifically in participants who described changes in drug or medication use. The whole model is presented without variable elimination. Data were analyzed using Stata version 14.2 statistical software (StataCorp LLC) and R version 3.4 (R Foundation for Statistical Computing). Statistical significance was tested at the conventional 5\% level.

**Ethics**

Ethical approval was gained from the Health Research Authority via the Integrated Research Application System (No. 235151).

**Results**

A total of 372 participants had previous COPD or ACO and were eligible for inclusion. The study follow-up took place between December 2017 and April 2018. Baseline questionnaire and clinical data were collected from 161 participants; 109 were lost to follow-up, 49 did not attend the follow-up appointment, 26 declined at the appointment, 23 were medically unfit, and four did not take part for other reasons. A total of 106 participants completed postbronchodilator spirometry at both baseline and follow-up to ATS standards. Patients remaining (n = 55) did not meet ATS standards (n = 22), were medically unfit (n = 3), died (n = 1), or declined postbronchodilator spirometry (n = 29) (Fig 1). Compression of participants characteristics can be seen in e-Table 1.

The characteristics of the population are given in Table 1. Participants had a mean age of 51 ± 5.3 years, and 46 (28.6\%) were women. Most participants were unemployed with high levels of socioeconomic deprivation (mean index of multiple deprivation score 51.5, which is in the lowest quintile for England). All

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**Figure 1** – Flow of participants through the study. ACO = asthma-COPD overlap; ATS = American Thoracic Society; GP = general practitioner.

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372 service users had previous diagnosed COPD or ACO and they
1) Were receiving a prescription for methadone or buprenorphine
2) Were under shared care between GP and drug service provider
3) Had previous spirometry with drug service provider since 2015

263 connected with their key worker and agreed to consider participation

161 consented to participate and met inclusion criteria

1 died
29 declined postbronchodilator spirometry
3 medically unfit

161 completed

49 did not attend
26 declined at the appointment
23 were medically unfit
1 did not met inclusion criteria
3 did not consent for other reasons

22 did not achieve postbronchodilator to ATS standard, declined completed only prebronchodilator spirometry

106 had baseline and follow-up postbronchodilator spirometry
participants were taking OST, with 76 (47.2%) reporting current heroin use.

Most were prescribed an inhaler and were collecting prescriptions (defined as at least 50% pickup rate) from a pharmacy (n = 131; 81.4%). No inhalers were prescribed or collected for 21 participants (13.3%), and data were unavailable for 9 participants (5.5%). Of the participants with available data, 129 (84.9%), 88 (57.9%), and 78 (51.3%) collected prescriptions for short-acting beta 2 agonist, long-acting muscarinic antagonist, and an inhaled corticosteroid/long-acting beta 2 agonist combination, respectively (Fig 2). Three-quarters had attended a primary care practitioner for respiratory complaints within the preceding 2 years, with 18 (11%) requiring admission to hospital, staying for a mean of 11.5 days. Participants admitted to hospital were universally treated with bronchodilators, antibiotics, and steroids; three participants were offered noninvasive ventilation; two were treated in high-dependency areas; and none had level 3 care (invasive ventilation) (Table 2).

The mean FEV₁ was 2.05 ± 0.96 L at follow-up compared with 2.23 ± 0.97 L at baseline. Of the participants diagnosed with COPD/ACO at baseline and postbronchodilator spirometry at both time points, 94 (88.7%) had spirometry indicative of COPD at follow-up, with 38 (35.9%) having severe or very severe COPD (using GOLD guidelines) at follow-up compared with 26 (24.6%) at baseline. A further five participants (4.7%) had full reversibility (> 400 mL) and therefore were diagnosed with asthma, and seven (6.6%) had normal spirometry at follow-up (Table 3).

Participants reported a significant annualized increase in respiratory symptoms with the MRC and CAT scores increasing by a median of 0.48 (P < .001) and 1.60 (P < .001), respectively. They experienced a significant annualized decline in FEV₁ and median oxygen

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**TABLE 1** Characteristics of 161 People With Baseline COPD or Asthma-COPD Overlap Derived From Follow-Up Questionnaire Data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, female</td>
<td>46 (28.6)</td>
</tr>
<tr>
<td>Age, y</td>
<td>51.0 ± 5.3</td>
</tr>
<tr>
<td>IMD score</td>
<td>51.5 ± 12.7</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>137 (85.1)</td>
</tr>
<tr>
<td>Employment</td>
<td>24 (14.9)</td>
</tr>
<tr>
<td>Housing</td>
<td></td>
</tr>
<tr>
<td>Own home (including rented)</td>
<td>124 (77.0)</td>
</tr>
<tr>
<td>Homeless</td>
<td>6 (3.7)</td>
</tr>
<tr>
<td>Other</td>
<td>31 (19.3)</td>
</tr>
<tr>
<td>Cigarette smoking status</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>133 (82.6)</td>
</tr>
<tr>
<td>Ex</td>
<td>27 (16.8)</td>
</tr>
<tr>
<td>Never</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Cigarettes smoked per day</td>
<td>11 ± 7.0</td>
</tr>
<tr>
<td>Heroin smoking status</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>76 (47.2)</td>
</tr>
<tr>
<td>Ex</td>
<td>85 (52.8)</td>
</tr>
<tr>
<td>Bags smoked per week</td>
<td>4.0 ± 7.0</td>
</tr>
<tr>
<td>Crack smoking</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>33 (20.5)</td>
</tr>
<tr>
<td>Ex</td>
<td>89 (55.3)</td>
</tr>
<tr>
<td>Never</td>
<td>39 (24.2)</td>
</tr>
<tr>
<td>Rocks smoked per week</td>
<td>2.18 ± 1.4</td>
</tr>
<tr>
<td>Cannabis smoking status</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>38 (23.8)</td>
</tr>
<tr>
<td>Ex</td>
<td>53 (33.1)</td>
</tr>
<tr>
<td>Never</td>
<td>69 (43.1)</td>
</tr>
<tr>
<td>Cannabis joint per week</td>
<td>12 ± 17.1</td>
</tr>
<tr>
<td>Ever injected heroin</td>
<td>30 (18.5)</td>
</tr>
<tr>
<td>Current methadone dosage, mL/d</td>
<td>45.7 ± 21.6</td>
</tr>
<tr>
<td>Current buprenorphine dosage, mg/d</td>
<td>10.4 ± 8.8</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or No. (%).

IMD = index of multiple deprivation.

* A bag is estimated to equate to 0.1 g.
Changes in smoking status and inhaler use were prehypothesized possible clinical factors that could influence FEV1 change. Since baseline, 49 participants (31.2%) reported a decrease in heroin smoking, and 73 (46.5%) reported unchanged usage (Fig 3). Change in drug use was not associated with change in FEV1. The final model showing change in drug and tobacco smoking status and inhaler use is presented in Table 5.

Discussion
In a population of heroin smokers, we found a high burden of lung disease. In the previously published baseline data, 50% of heroin users had COPD or ACO, with a mean MRC score of 3.1 and CAT score of 22.9. At follow-up, participants’ respiratory symptoms had worsened significantly from baseline, with annual increases in both CAT score (1.60) and MRC score (0.46), and mean oxygen saturation dropping from 97% to 95% from baseline to follow-up. We found that lung function measured by FEV1 declined by 90 mL annually, which was both statistically and clinically significant. The proportion of subjects classified as having severe or very severe disease increased from 25% to 36% over the 2-year follow-up period. Neither ongoing illicit drug use nor prescriptions of inhaled medication were associated with change in lung function.

The symptoms reported in this study are consistent with those of studies in this population, with increased dyspnea among heroin users being the common symptom. The decline in health status measured by a CAT score increase of 1.60 annually is greater than the 1 unit change seen in patients with stable COPD. The rate of decline in FEV1 is considerably higher than both the 30 mL/y age-related decline seen in nonsmokers and in people with tobacco-related COPD (which is reported at 35-79 mL/y, of which all but one paper reported an annual decline of ≤ 69 mL). To date, research on lung function in heroin smokers has focused on cross-sectional studies. The results from this longitudinal cohort study support and enhance previous cross-sectional studies that suggest heroin use.
users are at a high risk of COPD and suggest that their decline is worse than that of tobacco smokers. Walker et al\textsuperscript{11} found heroin smokers developed early onset emphysema, with a mean age of diagnosis being 41 years, suggesting likely early progression of disease compared with nonheroin smokers. In Amsterdam, The Netherlands, Buster et al\textsuperscript{14} reported a difference in FEV\textsubscript{1} from predicted values, finding that heroin smokers had an FEV\textsubscript{1} of 260 mL less than predicted FEV\textsubscript{1}.

The rapid decline in FEV\textsubscript{1} and the increase in respiratory symptoms in this population suggest heroin smoking is a driver of decline in lung function. Similarly, once established, this decline appears to continue even in people who stop smoking drugs.

Although COPD hospital admissions vary greatly across the United Kingdom, patients with COPD tend to have high health-care usage, particularly in areas of high deprivation.\textsuperscript{29,30} Previous research has also shown that heroin users with respiratory exacerbations are more likely to be readmitted with exacerbations than current/ex-tobacco smokers (OR, 1.00 vs 0.22/0.26, respectively).\textsuperscript{18} It is also clear that with the high levels of health-care access observed in this population, it is likely that ongoing trends toward inhaling heroin will further increase the use of, and burden on, the health system.\textsuperscript{4,6}

The strengths of our study include that we followed-up the participants over a 18- to 24-month period in a community clinic setting. We have shown that it is feasible to engage this client group in both baseline and follow-up spirometry allowing for a diagnosis to be made. The lost to follow-up rate is a major limitation of this study, reducing the power of statistical analysis and making stratification of our results by age or GOLD stage unfeasible. Given a larger group, this information would potentially be helpful for targeting care, and is an area for future investigation. This population tends to smoke a mix of heroin, crack, and tobacco, establishing a causal relationship with therefore difficult. The participants in the study were generally from a poor socioeconomic background, and there is potential that their living condition environment could contribute to the rate of decline. Without significant heterogeneity of such potentially confounding factors, we have been unable to address this question further. There is also potential for selection bias, with people who regularly attend methadone clinics and have concerns about their respiratory system more likely to participate in the study.

In summary, our findings show the significant respiratory impairment with which heroin smoking is implicated, and a concerning accelerated rate of decline over time. Future studies with larger cohorts, possibly in the context of a targeted public health intervention, are needed to understand if specific subgroups are especially vulnerable, and how the personal and health-care costs associated with chronic respiratory illness could be best averted. The study methodology is in support of it being feasible to colocate respiratory and drug services to one community location. Future studies may benefit from a parallel group of heroin

### Table 4

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Follow-Up</th>
<th>Change Per Year</th>
<th>Bootstrapping/95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV\textsubscript{1}, L</td>
<td>2.23 ± 97.12</td>
<td>2.05 ± 95.60</td>
<td>−0.09 ± 0.19</td>
<td>−0.05 to −0.13</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MRC score</td>
<td>3 (2-4)</td>
<td>4 (3-5)</td>
<td>0.46 (0.0 to 1.0)</td>
<td>0.52 (0.36 to 0.67)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CAT score</td>
<td>25 (17-31)</td>
<td>29 (23-33)</td>
<td>1.60 (−0.48 to 4.32)</td>
<td>0.46 (0.29 to 0.60)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SpO\textsubscript{2} (%)</td>
<td>97 (96-98)</td>
<td>95 (93-96)</td>
<td>−0.92 (−1.63 to 0.0)</td>
<td>0.53 (0.38 to 0.66)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Values are mean ± SD, median (25th percentile-75th percentile), or as otherwise indicated. CAT = COPD Assessment Tool; MRC = Medical Research Council Dyspnea Scale; SpO\textsubscript{2} = peripheral capillary oxygen saturation. See Table 3 legend for expansion of other abbreviation.

![Figure 3](https://example.com/figure3.png)

**Figure 3** – Change in daily consumption of tobacco, heroin, and crack in 161 subjects over 2 y. If they have never smoked, their smoking status was recorded as stayed the same.
users without spirometric abnormalities at baseline to determine their rate decline compared with patients with COPD. These results combined with previous studies support the call for enhanced screening for inhaled drug users. A pilot followed by clinical trial would be needed to assess if screening and treatment services would be clinically and cost-effective in this population.

Acknowledgments


Financial/nonfinancial disclosures: None declared.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Additional information: The e-Table can be found in the Supplemental Materials section of the online article.

References


Section 2: Supplement to Paper

Screening heroin smokers attending community drug clinics for change in lung function: A cohort study. Supplement

Supplement Table E1: Characteristics of participants completing follow up questionnaires, with and without ATS standard spirometry

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acceptable spirometry</th>
<th>Unacceptable spirometry or declined/excluded for medical reasons</th>
<th>Chi² or Ttest p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%), Mean (SD)</td>
<td>N (%), Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>30.2 (32)</td>
<td>25.5 (14)</td>
<td>0.53</td>
</tr>
<tr>
<td>Male</td>
<td>69.8 (74)</td>
<td>74.5 (41)</td>
<td></td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>50.9 (5.2)</td>
<td>51.3 (5.6)</td>
<td>0.67</td>
</tr>
<tr>
<td>IMD Score</td>
<td>50.3 (12.9)</td>
<td>53.9 (12.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>85.9 (91)</td>
<td>83.6 (46)</td>
<td>0.65</td>
</tr>
<tr>
<td>Employed</td>
<td>14.1 (15)</td>
<td>16.2 (9)</td>
<td></td>
</tr>
<tr>
<td>Housing</td>
<td></td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>Own home (inc. rental), n</td>
<td>77.4 (82)</td>
<td>76.4 (42)</td>
<td></td>
</tr>
<tr>
<td>Homeless, n (%)</td>
<td>4.72 (5)</td>
<td>1.82 (1)</td>
<td></td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>17.9 (19)</td>
<td>21.78 (12)</td>
<td></td>
</tr>
<tr>
<td>Cigarette Smoking Status</td>
<td></td>
<td></td>
<td>0.125</td>
</tr>
<tr>
<td>Current, n (%)</td>
<td>78.3 (83)</td>
<td>50 (90.9)</td>
<td></td>
</tr>
<tr>
<td>Ex, n (%)</td>
<td>22 (20.8)</td>
<td>5 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Never, n (%)</td>
<td>1 (0.9)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Heroin Smoking Status</td>
<td></td>
<td></td>
<td>0.312</td>
</tr>
<tr>
<td>Current, n (%)</td>
<td>44.34 (47)</td>
<td>52.7 (29)</td>
<td></td>
</tr>
<tr>
<td>Ex, n (%)</td>
<td>55.7 (59)</td>
<td>47.3 (26)</td>
<td></td>
</tr>
<tr>
<td>Crack smoking</td>
<td></td>
<td></td>
<td>0.74</td>
</tr>
<tr>
<td>Current, n (%)</td>
<td>18.9 (20)</td>
<td>23.6 (13)</td>
<td></td>
</tr>
<tr>
<td>Ex, n (%)</td>
<td>55.6 (59)</td>
<td>54.6 (30)</td>
<td></td>
</tr>
<tr>
<td>Never, n (%)</td>
<td>25.5 (27)</td>
<td>21.8 (12)</td>
<td></td>
</tr>
</tbody>
</table>
Section 3: PDF of IRAS Ethics Application
Please enter a short title for this project (maximum 70 characters)
COPD in Illicit Drug Users

1. Is your project research?
   - ☐ Yes  ☐ No

2. Select one category from the list below:
   - ☐ Clinical trial of an investigational medicinal product
   - ☐ Clinical investigation or other study of a medical device
   - ☐ Combined trial of an investigational medicinal product and an investigational medical device
   - ☐ Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
   - ☐ Basic science study involving procedures with human participants
   - ☐ Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
   - ☐ Study involving qualitative methods only
   - ☐ Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
   - ☐ Study limited to working with data (specific project only)
   - ☐ Research tissue bank
   - ☐ Research database

If your work does not fit any of those categories, select the option below:
   - ☐ Other study

2a. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?
   - ☐ Yes   ☐ No

2b. Please answer the following question(s):
   a) Does the study involve the use of any ionising radiation?
      - ☐ Yes  ☐ No
   b) Will you be taking new human tissue samples (or other human biological samples)?
      - ☐ Yes  ☐ No
   c) Will you be using existing human tissue samples (or other human biological samples)?
      - ☐ Yes  ☐ No

Date: 18/09/2017
d) Will the study involve any other clinical procedures with participants (e.g. MRI, ultrasound, physical examination)?  

3. In which countries of the UK will the research sites be located? (Tick all that apply)

☑ England
☐ Scotland
☐ Wales
☐ Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

☑ England
☐ Scotland
☐ Wales
☐ Northern Ireland
☐ This study does not involve the NHS

4. Which applications do you require?

IMPORTANT: If your project is taking place in the NHS and is led from England select 'IRAS Form'. If your project is led from Northern Ireland, Scotland or Wales select 'NHS/HSC Research and Development Offices' and/or relevant Research Ethics Committee applications, as appropriate.

☑ IRAS Form
☐ Confidentiality Advisory Group (CAG)
☐ National Offender Management Service (NOMS) (Prisons & Probation)

For NHS/HSC R&D Offices in Northern Ireland, Scotland and Wales the CI must create NHS/HSC Site Specific Information forms, for each site, in addition to the study wide forms, and transfer them to the PIs or local collaborators.

For participating NHS organisations in England different arrangements apply for the provision of site specific information. Refer to IRAS Help for more information.

Most research projects require review by a REC within the UK Health Departments' Research Ethics Service. Is your study exempt from REC review?

☐ Yes  ☐ No

5. Will any research sites in this study be NHS organisations?

☐ Yes  ☐ No

6. Do you plan to include any participants who are children?

☐ Yes  ☐ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

☐ Yes  ☐ No

Date: 18/09/2017
Answer: Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

☐ Yes ☐ No

9. Is the study or any part of it being undertaken as an educational project?

☐ Yes ☐ No

Please describe briefly the involvement of the student(s):
I am a PhD student and will act as the Principle Investigator

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

☐ Yes ☐ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

☐ Yes ☐ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

☐ Yes ☐ No
Integrated Research Application System
Application Form for Basic science study involving procedures with human participants

Please refer to the E-Submission and Checklist tabs for instructions on submitting this application.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familiar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
COPD in Illicit Drug Users

Please complete these details after you have booked the REC application for review.

REC Name:
London Riverside

REC Reference Number: 17/lo/1697
Submission date: 18/09/2017

PART A: Core study information

A1. Full title of the research:
COPD IN ILLICIT DRUG USERS:
How does severity and progression predict healthcare seeking and treatment?

A2-1. Educational projects
Name and contact details of student(s):

<table>
<thead>
<tr>
<th>Student 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title: Forename/Initials Surname</td>
</tr>
<tr>
<td>Mrs Rebecca Nightingale</td>
</tr>
<tr>
<td>Address: MRC DTP student</td>
</tr>
<tr>
<td>LSTM, Pembroke Place</td>
</tr>
<tr>
<td>Liverpool</td>
</tr>
<tr>
<td>Post Code: L3 5QA</td>
</tr>
<tr>
<td>E-mail: <a href="mailto:rebecca.nightingale@lstm.ac.uk">rebecca.nightingale@lstm.ac.uk</a></td>
</tr>
<tr>
<td>Telephone: 07702812183</td>
</tr>
<tr>
<td>Fax:</td>
</tr>
</tbody>
</table>

Give details of the educational course or degree for which this research is being undertaken:

Date: 18/09/2017
Name and level of course/degree:
PhD Liverpool School of Tropical Medicine.

Name of educational establishment:
Liverpool School of Tropical Medicine

Name and contact details of academic supervisor(s):

**Academic supervisor 1**

<table>
<thead>
<tr>
<th>Title</th>
<th>Forename/Initials</th>
<th>Surname</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr</td>
<td>Jamie</td>
<td>Rylance</td>
</tr>
</tbody>
</table>

**Address**

LSTM, Pembroke Place
Liverpool

**Post Code**

L3 5QA

**E-mail**

jamie.rylance@lstmed.ac.uk

**Telephone**

07904242353

**Fax**


**Academic supervisor 2**

<table>
<thead>
<tr>
<th>Title</th>
<th>Forename/Initials</th>
<th>Surname</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr</td>
<td>Kevin</td>
<td>Mortimer</td>
</tr>
</tbody>
</table>

**Address**

LSTM, Pembroke Place
Liverpool

**Post Code**

L3 5QA

**E-mail**

Kevin.Mortimer@lstmed.ac.uk

**Telephone**

07980 958309

**Fax**


Please state which academic supervisor(s) has responsibility for which student(s):
Please click "Save now" before completing this table. This will ensure that all of the student and academic supervisor details are shown correctly.

<table>
<thead>
<tr>
<th>Student(s)</th>
<th>Academic supervisor(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Student 1</td>
<td>Mrs Rebecca Nightingale</td>
</tr>
<tr>
<td></td>
<td>Dr Jamie Rylance</td>
</tr>
<tr>
<td></td>
<td>Dr Kevin Mortimer</td>
</tr>
</tbody>
</table>

A copy of a current CV for the student and the academic supervisor (maximum 2 pages of A4) must be submitted with the application.

A2.2. Who will act as Chief Investigator for this study?

- [ ] Student
- [ ] Academic supervisor
- [ ] Other

Date: 18/09/2017
A3-1. Chief Investigator:

<table>
<thead>
<tr>
<th>Title Forname/Initials Surname</th>
<th>Mrs Rebecca Nightingale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post</td>
<td>PhD Student (MRC DTP)</td>
</tr>
<tr>
<td>Qualifications</td>
<td>Bsc Physiotherapy</td>
</tr>
<tr>
<td></td>
<td>Msc Global Health and Development</td>
</tr>
<tr>
<td></td>
<td>Mres clinical science</td>
</tr>
<tr>
<td></td>
<td>GCP</td>
</tr>
<tr>
<td>ORCID ID</td>
<td>0000 0001 5638 8531</td>
</tr>
<tr>
<td>Employer</td>
<td>Liverpool School of Tropical Medicine</td>
</tr>
<tr>
<td>Work Address</td>
<td>MRC DTP student</td>
</tr>
<tr>
<td></td>
<td>LSTM, Pembroke Place</td>
</tr>
<tr>
<td>Post Code</td>
<td>L3 5QA</td>
</tr>
<tr>
<td>Work E-mail</td>
<td><a href="mailto:rebecca.nightingale@lstmmed.ac.uk">rebecca.nightingale@lstmmed.ac.uk</a></td>
</tr>
<tr>
<td>* Personal E-mail</td>
<td><a href="mailto:beckyq1983@hotmail.com">beckyq1983@hotmail.com</a></td>
</tr>
<tr>
<td>Work Telephone</td>
<td></td>
</tr>
<tr>
<td>* Personal Telephone/Mobile</td>
<td>07702812183</td>
</tr>
<tr>
<td>Fax</td>
<td></td>
</tr>
</tbody>
</table>

* This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent. A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project? This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

| Title Forname/Initials Surname | Mr Carl Henry |
| Address                       | Liverpool School of Tropical Medicine |
|                              | Pembroke Place |
|                              | Liverpool     |
| Post Code                     | L3 5QA        |
| E-mail                        | lstmrec@lstmmed.ac.uk |
| Telephone                     | 01517028396   |
| Fax                           | 01517053370   |

A5-1. Research reference numbers. Please give any relevant references for your study:

- Applicant's/organisation's own reference number, e.g. R & D (if available): 17-055
- Sponsor's/protocol number: 17-055
- Protocol Version: v1
- Protocol Date: 01/09/2017
- Funder's reference number:
- Project website:

Registry reference number(s):
The Department of Health's Research Governance Framework for Health and Social Care and the research governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials.

Date: 18/09/2017
Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject", and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):
ClinicalTrials.gov identifier (NCT number):

**Additional reference number(s):**

<table>
<thead>
<tr>
<th>Ref. Number</th>
<th>Description</th>
<th>Reference Number</th>
</tr>
</thead>
</table>

**A5-2. Is this application linked to a previous study or another current application?**

☐ Yes ☐ No

Please give brief details and reference numbers.

**A6-1. Summary of the study.** Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments’ Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.

Aim of the study: To determine the rate of decline in lung function in illicit drug users in Liverpool. In addition, to determine severity and progression of chronic lung disease and its relationship with acute health care seeking in illicit drug users (particularly those smoking heroin) with known COPD in Liverpool.

Background: Illicit drugs users, particularly heroin smokers appear to have increased risk of acute presentations with respiratory disease, however tend not to present to available primary care facilities. In areas with a high number of illicit drugs users such as Liverpool, this puts an increased burden on acute respiratory services and A & E departments. The individual is likely to experience poorer continuity of care if they repeatedly use different acute services rather than primary care. Despite this there are few studies that focus on illicit drug users with COPD. There are no longitudinal studies that document their lung function patterns or how this relates to their acute health needs. This information is required to develop care pathways that focus on improving care and delivering a quality service to people who have real healthcare needs.

Methods: A cohort study of over 18 year-olds that have previous accessible spirometry and attend Addaction clinics in Liverpool. Addaction (https://www.addaction.org.uk) provide treatment services on behalf of the NHS for illicit drug users. Spirometry will be collected and compared to previous spirometry results. A questionnaire and their medical and drugs history will be used to assess for health care usage during the follow-up period (approximately 12-18 months). In addition, 10 individuals will participate in a structured interview which will be used gain a rich experiential understanding of participants’ healthcare needs, service utilization, and perception of quality of care. The study will take place between October 2017 and January 2019.

**A6-2. Summary of main issues.** Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, HRA, or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.
The participants: The participants are potentially a vulnerable group. To help with this the spirometry and questionnaire will be done in Addaction clinics with key workers who know the participants well and are aware of their vulnerabilities and any risks. The participants will be seen for this study in normal clinic time, so they will not need to come into a clinic specially to be part of the study, unless they are one of the 10 that asked to take part in qualitative interviews. If they have respiratory problems they can be referred to their GP and also offered services that Addaction provide.

Spirometry: Participants will be prescribed spirometry by a qualified medical doctor who knows the patients and works for Addaction. This is to ensure that any contraindications that could make spirometry unsafe are checked prior to spirometry taking place. Spirometry will be carried out by registered health professionals.

Inclusion/Exclusion: Participants are only excluded if it would be unsafe for them to carry out the spirometry.

Medical records review: Only data relating to the participants' respiratory history will be recorded. This will be a review of the notes 2 year prior to study date and up until 30th January 2019. Only the the named research team will review the notes and data will be kept anonymised linked only by the participants' ID.

A7. Select the appropriate methodology description for this research. Please tick all that apply:

- [ ] Case series/ case note review
- [ ] Case control
- [x] Cohort observation
- [ ] Controlled trial without randomisation
- [ ] Cross-sectional study
- [ ] Database analysis
- [ ] Epidemiology
- [ ] Feasibility/ pilot study
- [ ] Laboratory study
- [ ] Metanalysis
- [x] Qualitative research
- [x] Questionnaire, interview or observation study
- [ ] Randomised controlled trial
- [ ] Other (please specify)

A10. What is the principal research question/objective? Please put this in language comprehensible to a lay person.

Primary Objective: To determine the change in lung function, health status and symptoms in illicit drug users with COPD in Liverpool, UK; 1.5-2.5 years from baseline when diagnosed or diagnosis confirmed (baseline collected as part of a new service development in 2015/2016).

A11. What are the secondary research questions/objectives if applicable? Please put this in language comprehensible to a lay person.

Secondary Objective: To assess the relationship between diagnosis or confirmation of chronic lung disease (COPD and asthma) in illicit drug users and health care usage and treatment.

A12. What is the scientific justification for the research? Please put this in language comprehensible to a lay person.

Liverpool has the highest numbers of drug related deaths of any town in the UK, with an estimated 1.5% of the population regularly using illicit drugs.
Although the ill-effects of drug use are widely documented, there is limited evidence surrounding the chronic effects of drug use on the respiratory system. For the past three decades heroin has predominantly been smoked rather than injected. It is known that people who smoke heroin are at risk of COPD but are infrequently diagnosed or treated. Although they smoke tobacco as well, heroin smokers frequently develop severe symptomatic COPD decades before tobacco smokers.

Multiple case reports highlight acute asthma attacks in heroin users, and observational studies report a high prevalence of respiratory disease in heroin users admitted to acute hospitals. Chronic respiratory diseases measured by lung function testing are less well documented. One cross-sectional study in Amsterdam of 100 participants recruited from methadone clinics found that those who smoked heroin had increased odds of dyspnoea and impaired lung function. The study was conducted using a relatively small population size and many participants also smoked tobacco. Participants were not followed up over time, and therefore it is difficult to make inferences about the nature and progression of the apparent chronic respiratory symptoms. To date no longitudinal studies documenting the outcome of lung function tests in heroin users in the UK can be found. This study will provide spirometry data over a two period on illicit drug users (particularly heroin users) with known COPD. This will add to the scientific knowledge in this area and allow clinicians to know how their patients are likely to progress with the disease. This is already known for tobacco smokers and the general population with COPD, but not those who have COPD because of heroin and other illicit drug smoking.

Although a high rate of acute admissions amongst illicit drug users is well documented, little evidence is available surrounding the health care needs and behaviour of this group of patients. We also know that drugs users, particularly heroin smokers, appear to have increased risk of acute presentations with respiratory disease, however tend not to present to available primary care facilities. The pattern and reasons for the lack of primary health care usage are not fully understood and within Liverpool there have been no studies that specifically investigate drug users with chronic lung disease.

This study will take place in collaboration with Addiction. Addiction provides keyworkers for Opiate Substitution Therapy (OST) and prescriptions for methadone (or occasionally buprenorphine) are either provided by clients’ GPs (shared care with Addiction and Primary care) or Addiction clinicians.

Historically, UK drug policy has focused on harm reduction which replaces illegally purchased heroin with prescribed opiates, usually methadone (OST). Emphasis has more recently moved towards recovery and overcoming addiction[10]. Addiction works with clients within Liverpool to provide these services. OST is linked to a programme which integrates addiction treatment, better social functioning and management of physical and mental health problems. This is orchestrated through substance misuse clinics. Methadone prescription is contingent on regular interaction between an individual and their drug keyworker. Heroin smokers often have chaotic lifestyles and engage ineffectively with traditional health services seeking acute care when unwell but infrequently attending appointments for routine care. Their most consistent, and sometimes only, point of contact with healthcare services is the substance misuse clinic - their 'anchor point'. This study will repeat spirometry which was previously successfully provided at the ‘anchor point’, in Addiction clinics, as part of a screening programme / service modification. In the future this may be a way to provide respiratory care to these clients.

A13. Please summarise your design and methodology. It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.

Hypothesis:
Illicit drug users will have a faster rate of decline in lung function than the known documented rate of decline in a general COPD population. Those with worse severity of chronic lung disease will access acute health care services more than those with mild disease. Those with severe disease tend to access care through hospitals rather than community routes.

Method:
Participants will be recruited via Addiction clinics where support can be provided to them and key workers know them as individuals.

Consent will take place in the Addiction clinics once the participants has had time to read and understand the information sheet. If they decline to participate it will not in any way affect their Addiction care.

The spirometry and questionnaire will then take place in clinic at a time when the participant will be coming any way for follow up. The participant will be asked to blow into the spirometer 2-5 times and then be given a salbutamol inhaler. 20 minutes later they will again be asked to blow into the spirometer. During the 20 mins the participant will be asked the conclusion questionnaire and an MRC and CAT score will be completed. Overall this part of the study will take approximately 30 minutes.

10 participants will be asked if they are prepared to take part in further structured interviews conducted by Dr Paul Griffiths, which will be arranged at a time convenient to the participant. The interview will take 30-45 minutes. They will
also take place in the Addaction clinic. Once consented, named members of the study team will review the medical records of the participants; this will be for 2 years prior to this study up to 30th January 2019. The reason for this is to avoid the recall bias that is likely as the study relies on self-reported episodes of acute care use and inhaler prescription. For details of the items collected from the medical records please see COPD in Illicit Drug Users: Coding for Medical Record Access V-1 (date 1/9/2017).

A14.1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

☐ Design of the research
☐ Management of the research
☐ Undertaking the research
☐ Analysis of results
☐ Dissemination of findings
☐ None of the above

Give details of involvement, or if none please justify the absence of involvement.
The Addaction clients were asked as part of service improvement if they would be interested and happy to consider participating in further research that allowed them to access respiratory services in the clinic or ‘anchor point’. They were previously positive about this.

The findings will be disseminated to the clients that use Addaction via Addaction staff and key workers. The results will be explained to all Addaction staff by members of the research team to ensure accurate information is given to both the participants and other Addaction clients.

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

☐ Blood
☐ Cancer
☐ Cardiovascular
☐ Congenital Disorders
☐ Dementias and Neurodegenerative Diseases
☐ Diabetes
☐ Ear
☐ Eye
☐ Generic Health Relevance
☐ Infection
☐ Inflammatory and Immune System
☐ Injuries and Accidents
☐ Mental Health
☐ Metabolic and Endocrine
☐ Musculoskeletal
A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

Adults over the age of 18 years.
Currently attending Addiction clinics in Liverpool.
Had previous spirometry in Addiction clinics - in order that this spirometry done in this study can be compared to previous spirometry done as part of a service development.
Fluent spoken English - to ensure a comprehensive understanding of the research project and their proposed involvement.
Capacity to give informed consent.

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

Unable to safely take part in spirometry (Including active or recent hemoptysis; current or history of pneumothorax; Myocardial infarction with the last month; current pulmonary embolism; hemorrhagic cerebrovascular event; recent thoracic, abdominal or eye surgery; current vomiting; severe chest pain; confusion; recent middle-ear infection; active TB)
Allergy or unable to take Salbutamol
No previous spirometry with Addiction
Acute confusion or intoxication

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. These include seeking consent, interviews, non-clinical observations and use of questionnaires.

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

<table>
<thead>
<tr>
<th>Intervention or procedure</th>
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<th>3</th>
<th>4</th>
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<tr>
<td>Consent</td>
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<td>15 mins</td>
<td>The project PI with Addaction keyworkers in the Addaction clinic</td>
</tr>
<tr>
<td>Standardised questionnaires (MRC and CAT Score)</td>
<td>1</td>
<td>1</td>
<td>15 mins</td>
<td>Completed by the PI in the Addaction clinic, between pre and post spirometry.</td>
</tr>
<tr>
<td>Qualitative interview for 10 participants only</td>
<td>1</td>
<td>0</td>
<td>45 mins</td>
<td>Completed by Dr Paul Griffiths, a member of the research team, in the Addaction clinic.</td>
</tr>
</tbody>
</table>
A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

<table>
<thead>
<tr>
<th>Intervention or procedure</th>
<th>1</th>
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<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
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<td>Pre and post bronchodilator</td>
<td>1</td>
<td>1</td>
<td>30</td>
<td>mins</td>
</tr>
</tbody>
</table>
| spirometry                        |   |   |   | clinic.

A21. How long do you expect each participant to be in the study in total?

The participants will only need to attend one clinic as part of their normal Addacation reviews. They will be included in the study for approximately 12-18 months but this will involve the study team reviewing their medical notes and will not involve participants’ time.

There will be 10 participants who will each be asked if they will return to clinic and take part in one 45 min interview. This will take place between November 2017 and May 2018.

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

There are minimal risks. Spirometry is performed regularly as part of routine respiratory care and will not be performed on anyone where it is unsafe to do so. Participants may be anxious about the results, and this is why we have ensured the clinics take place in Addacation clinics where a keyworker is present.

We will schedule appointments as part of their Addacation clinic care so there should be minimal disruption to their lifestyle.

All data collected from medical notes will be related to respiratory care only and linked only via participants’ ID numbers. The participant will be given as much time as is required to understand the study and if they are uncomfortable with this information being gathered they are under no obligation to participate, and it will not affect their Addacation care.

Addacation will be involved throughout the study to ensure their clients are not inconvenienced or feel that there is significant intrusion on them personally or their lifestyle.

A24. What is the potential for benefit to research participants?

There are no direct benefits to the participant when taking part in the study. Participants may benefit from a better understanding of clinical research, and they may also benefit from a sense of contributing to medical research in a very valuable way. They may benefit from their GPs being aware of spirometry results and future care that is given to them indirectly through this study.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources
will be used? For example, identification may involve a disease register, computerized search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).

Potential participants will be identified by the care team at Addaction, based on those participants who have previously done spirometry in the Addaction clinics. We will also advertise the study in GP surgeries and public sites so that potential participants can get in touch with Addaction keyworkers if they would like to take part. The research team will only see the details of those who could potentially take part. They will not look through the general Addaction databases.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

☐ Yes  ☐ No

Please give details below:
The name and contact details of participants will be required in order to book the clinic appointment but this will all be done by Addaction staff who would be booking their clinic as routine clinical work and are part of their clinical team.

A27-3. Describe what measures will be taken to ensure there is no breach of any duty of confidentiality owed to patients, service users or any other person in the process of identifying potential participants. Indicate what steps have been or will be taken to inform patients and service users of the potential use of their records for this purpose. Describe the arrangements to ensure that the wishes of patients and service users regarding access to their records are respected. Please consult the guidance notes on this topic.

The Addaction team will use their database to contact patients. This is a database that contains a list of those who had previous spirometry in their clinics as part of a service development. Addaction have access to these details as part of routine work in order to book clinics and as part of routine care given to their patients. The research team will only have access to the information once the participant has consented to take part in the this study and has consented for their previous records to be access by the research team.

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

☐ Yes  ☐ No

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

☐ Yes  ☐ No

If Yes, please give details of how and where publicity will be conducted, and enclose copy of all advertising material (with version numbers and dates).

Posters will be put up in GP surgeries and key sites so that potential participants can get in touch with Addaction keyworkers.

A29. How and by whom will potential participants first be approached?

Participants will be approached by the Addaction key worker or the project manager named for the project. The first contact will always be through Addaction staff who know the participant. Contact will either be made in routine clinic appointments or via telephone as part of booking a clinic appointment.

A30-1. Will you obtain informed consent from or on behalf of research participants?

☐ Yes  ☐ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for
children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

Participants will be given an information sheet to read. They will be given as much time as they wish to decide if they want to take part. A member of the Addiction staff who is protocol trained will explain the study to the participant. If they wish to consent, consenting will take place in the Addiction clinic by the principle investigator or member of research team. Addiction keyworkers will be available in clinics and it will be made clear to the participants that there is no obligation to take part and it will not affect any future care given to them.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

☐ Yes  ☐ No

A31. How long will you allow potential participants to decide whether or not to take part?

Participants will be given time to consent; as long as they consent within the period for collecting the spirometry - which is likely to be April 2018 - they will be able to take part. Some participants may wish to take part at the same clinic slot as they are asked about the study. If the participant has fully read the information sheet and the keyworker and PI are satisfied that the participant understands the study, the study could take place. An example of this may be for a patient known to Addiction who does not attend clinic often and would rather complete the study in the current clinic than a clinic date that is many weeks later.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

☐ Yes  ☐ No  ☐ Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

The participants can be asked by Addcuation staff if they are taking part in other research, which should also be recorded on their Addiction records. We are aiming not to include participants they are involved in other studies but it is not set as part of the exclusion criteria.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? (e.g. translation, use of interpreters)

The Addiction staff will be available to read the information sheet and consent form to those who can’t understand written English. Being able to speak English is part of the inclusion criteria as interpreters are not always available in Addcations clinics.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? Tick one option only.

☐ The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.

☐ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.

☐ The participant would continue to be included in the study.

☐ Not applicable – informed consent will not be sought from any participants in this research.
Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

**Further details:**
The participant is only required to visit the clinic for research purposes once unless they are part of the qualitative interviews. If at any stage of the face to face contact the participant loses capacity to consent they will be withdrawn from the study. However at the face-to-face time it will not be practical for the research team to monitor their capacity, this is during the phase when the researchers are reviewing their medical notes. Continued capacity is will therefore be assumed.

*If you plan to retain and make further use of identifiable data/tissue following loss of capacity, you should inform participants about this when seeking their consent initially.*

### Confidentiality

In this section, not all data may be uniquely relating to a participant who could potentially be identified if subject to a breach, e.g. if an address or telephone number were linked to a participant through previous consent.

### Storage and use of personal data during the study

**A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?** *(Tick as appropriate)*

- [x] Access to medical records by those outside the direct healthcare team
- [ ] Access to social care records by those outside the direct social care team
- [ ] Electronic transfer by magnetic or optical media, email or computer networks
- [ ] Sharing of personal data with other organisations
- [ ] Export of personal data outside the EEA
- [ ] Use of personal addresses, postcodes, faxes, emails or telephone numbers
- [x] Publication of direct quotations from respondents
- [ ] Publication of data that might allow identification of individuals
- [x] Use of audio/visual recording devices
- [ ] Storage of personal data on any of the following:
  - [x] Manual files (includes paper or film)
  - [ ] NHS computers
  - [ ] Social Care Service computers
  - [ ] Home or other personal computers
  - [ ] University computers
  - [ ] Private company computers
  - [ ] Laptop computers

**Further details:**
Medical history and continued acute care visits:
Participants will be asked to consent to researchers reviewing their primary care and health care records for 2 years prior to the study and until January 2019. The data collected will only be used to review relevant respiratory medical events (including admission to A&E for respiratory conditions, prescriptions of antibiotics and inhalers, and respiratory diagnostic tests such as X-rays). This will be accessed via EMIS (the electronic primary healthcare records in Liverpool) and from acute admissions to the Royal Liverpool and Broadgreen University Hospital Trust and Aintree University Hospitals Trust.

All data collected will be anonymised and collected on a proforma form, and will be stored on a password protected...
and encrypted spreadsheet. Access will stop after 31st January 2019. Direct quotes maybe used from the write up of the qualitative side of this project but will be completely anonymised with no initials or names used. Any recording will be voice only and will not include the use of participants’ names. Participants will be identifiable on any recording via the participant ID number. Manual forms will be stored in a locked cabinet in a locked room at per the data storage policy for Liverpool School of Tropical Medicine.

A37. Please describe the physical security arrangements for storage of personal data during the study?

Data will be stored on password protected and encrypted computers to industry standards. Data on the main database will be anonymised with linking only via participants ID. Data that is in paper format will be stored in locked rooms and locked at Liverpool School of Tropical Medicine (LSTM).

A38. How will you ensure the confidentiality of personal data? Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.

All data will be handled in accordance with LSTM Research Data Management Policy and Data Protection Act Policy and within the ICT Security Policy. Once collected data will be anonymised on the main database using only participants’ ID numbers. All paper consent forms will be kept in locked rooms and locked cabinets at LSTM. The Principal Investigators will maintain all records and documents regarding the conduct of the study and retain these for at least 7 years, or for longer if required. The Study Master File and study documents will be finally archived at secure archive facilities at LSTM.

A40. Who will have access to participants’ personal data during the study? Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.

The research team will have access to participants’ personal data but only once they have provided for this to take place. This is to allow the relevant research team members as listed in the protocol to follow up the participants’ medical history until January 2019. This is fully documented in the information sheet and will only be done by members of research team. The members who will be doing this are health professionals who have all completed confidentiality agreements as part of their job roles.

A41. Where will the data generated by the study be analysed and by whom?

Data will be analysed by members of the research team within Liverpool or Lancaster. All data that is analysed will be anonymised. No data will be transferred outside of the research team or the UK.

A42. Who will have control of and act as the custodian for the data generated by the study?

<table>
<thead>
<tr>
<th>Title</th>
<th>Forename/Initials</th>
<th>Surname</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr</td>
<td>Jamie</td>
<td>Rylance</td>
</tr>
<tr>
<td>Post</td>
<td>Senior Lecturer in Respiratory Medicine</td>
<td></td>
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<td></td>
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<td></td>
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<td>Post Code</td>
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<tr>
<td>Work Email</td>
<td>07904242353</td>
<td></td>
</tr>
</tbody>
</table>

Date: 18/09/2017
A43. How long will personal data be stored or accessed after the study has ended?

○ Less than 3 months
○ 3 – 6 months
○ 6 – 12 months
○ 12 months – 3 years
○ Over 3 years

A44. For how long will you store research data generated by the study?

Years: 7
Months: 0

A45. Please give details of the long term arrangements for storage of research data after the study has ended. Say where data will be stored, who will have access and the arrangements to ensure security.

The Principal Investigators will maintain all records and documents regarding the conduct of the study and retain these for at least 7 years or for longer if required. The Study Master File and study documents will finally be archived at secure archive facilities at LSTM.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

○ Yes  ○ No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

○ Yes  ○ No

A48. Does the Chief Investigator or any other Investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes  ○ No

INFORMATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants’ General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

○ Yes  ○ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

Date: 18/09/2017
A45.2. Will you seek permission from the research participants to inform their GP or other health/care professional?

☐ Yes  ☐ No

*It should be made clear in the participant's information sheet if the GP/health professional will be informed.*

**PUBLICATION AND DISSEMINATION**

A50. Will the research be registered on a public database?

*The Department of Health's Research Governance Framework for Health and Social Care and the research governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials. Furthermore, Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.*

☐ Yes  ☐ No

*Please give details, or justify if not registering the research.*

This is not a full clinical trial. It involves completing spirometry but otherwise is not a random controlled trial. This is a small part of a larger PhD and is for education purposes. The study is completed via Addaction who will register the study with their research and development department, but it will not be registered external to this.

*Please ensure that you have entered registry reference number(s) in question A51-1.*

A51. How do you intend to report and disseminate the results of the study? *Tick as appropriate:*

- ☑ Peer reviewed scientific journals
- ☑ Internal report
- ☑ Conference presentation
- ☑ Publication on website
- ☐ Other publication
- ☐ Submission to regulatory authorities
- ☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- ☐ No plans to report or disseminate the results
- ☐ Other (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

The data will be anonymised when analysed and therefore there will be no personal data used. All recordings of interviews will only contain the participants' ID number and no names, initials or ID numbers will be used in the write up or publications.

A53. Will you inform participants of the results?

☐ Yes  ☐ No

*Please give details of how you will inform participants or justify if not doing so.*

Addaction staff will be informed of the results and will be able disseminate these to participants.
A54. How has the scientific quality of the research been assessed? Tick as appropriate:

- [x] Independent external review
- [ ] Review within a company
- [ ] Review within a multi-centre research group
- [x] Review within the Chief Investigator's institution or host organisation
- [x] Review within the research team
- [ ] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review.

The study has been reviewed by my PhD supervisor, and also by LSTM's Research and Governance department. The study was also subject to a PhD defense commit panel which included three external experts. The study was passed to be part of my wider PhD project. The study has also been reviewed by the Addiction clinical lead and by members of the Addiction team.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? Tick as appropriate:

- [ ] Review by independent statistician commissioned by funder or sponsor
- [ ] Other review by independent statistician
- [ ] Review by company statistician
- [ ] Review by a statistician within the Chief Investigator's institution
- [x] Review by a statistician within the research team or multi-centre group
- [ ] Review by educational supervisor
- [ ] Other review by individual with relevant statistical expertise
- [ ] No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

Title  Forename/Initials  Surname
Mr  Emanuele  Girogi

Department  CHICAS
Institution  University of Lancaster
Work Address  Bailrigg
              Lancaster

Post Code  LA1 4YW
Telephone
Fax
Mobile  07453286122
E-mail  e.girogi@lancaster.ac.uk

Date: 18/09/2017
Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?
FEV1 decline as a measure of lung function decline from baseline.

A58. What are the secondary outcome measures? (if any)
Reporting the patterns of health care usage with a population of illicit drugs users with known COPD.
Determine how the severity of lung disease may predict health care usage
Use the information to design a care pathway for this group of patients.

A59. What is the sample size for the research? How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.
Total UK sample size: 360
Total international sample size (including UK):
Total in European Economic Area:
Further details:

A60. How was the sample size decided upon? If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.
Based on standard COPD spirometry decline rates of between 30-60ml with SD 150-250 the power calculations are shown in table one. If an assumption of a minimum of a 30ml decline per year is made with a maximum SD of 200ml, a sample of 300 is needed to achieve power of over 0.95. Assuming a 20% drop out rate we will aim to recruit 360 participants to this study.

A61. Will participants be allocated to groups at random?
☐ Yes  ☐ No

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.
This study aims to determine the rate of decline in lung function in participants who use illicit drugs. We aim to quantify the rate of decline.
Primary outcome analysis:
The primary endpoint will be summarised as a rate of decline in FEV1 and FVC. A mixed effects regression model will be used to include potential risk factors such as smoking of tobacco.
Secondary outcomes analysis:
Report the severity of disease seen as measured by clinical factors such as MRC dyspnea score, CAT scale and spirometry.
Determine how severity measured by clinical factors such as MRC dyspnea score, CAT scale, lung function impacts on health care usage.
Report the change in health care usage in participants from 2 years before the study to end of January 2019.
Report participant's experience of respiratory disease in relation to health care usage and medication usage.
Quantitative analysis will be used using a mixed effect regression model, odds ratios and linear model as appropriate.
Qualitative analysis will be done via thematic coding and triangulation of results.
A63. **Other key investigators/collaborators.** Please include all grant co-applicants, protocol co-authors and other key members of the Chief Investigator’s team, including non-doctoral student researchers.

<table>
<thead>
<tr>
<th>Title</th>
<th>Forename/Initials</th>
<th>Surname</th>
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<tbody>
<tr>
<td>Dr</td>
<td>Jamie</td>
<td>Rylance</td>
</tr>
</tbody>
</table>

**Post**  
Senior Clinical Lecturer in Respiratory Medicine, Honorary Consultant in Respiratory Medicine

**Qualifications**  
DMBS  
DTM&H  
MRCP  
PhD

**Employer**  
Liverpool School of Tropical Medicine

**Work Address**  
LSTM, Pembroke Place  
Pembroke Place  
Liverpool

**Post Code**  
L3 5QA

**Telephone**  
07904242353

**Fax**

**Mobile**  
07904242353

**Work Email**  
jamie.rylance@lstm.ac.uk

<table>
<thead>
<tr>
<th>Title</th>
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</thead>
<tbody>
<tr>
<td>Dr</td>
<td>Kevin</td>
<td>Mortimer</td>
</tr>
</tbody>
</table>

**Post**  
Reader

**Qualifications**  
BA MA MB BCHir FRCP DTM&H MSc PhD

**Employer**  
Liverpool School of Tropical Medicine

**Work Address**  
LSTM, Pembroke Place  
Pembroke Place

**Post Code**  
L3 5QA

**Telephone**

**Fax**

**Mobile**  
07980958309

**Work Email**  
kevin.mortimer@lstm.ac.uk

<table>
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<th>Title</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Dr</td>
<td>Hassan</td>
<td>Burhan</td>
</tr>
</tbody>
</table>

**Post**  
Consultant Respiratory Physician

**Qualifications**  
MBChB FRCP

**Employer**  
Royal Liverpool University Hospital

**Work Address**  
Respiratory Medicine  
Link 6Z  
Liverpool

**Post Code**  
L7 8XP

**Telephone**  
07828222452

**Fax**

**Mobile**

**Work Email**
Title Forename/Initials Surname
Dr Paul Griffiths

Post
Respiratory Registrar

Qualifications
MBChB (Hons), MRCP (UK)

Employer
Liverpool Heart and Chest Hospital

Work Address
Department of Respiratory Medicine
Liverpool Heart and Chest Hospital

Post Code
L14 3PE

Telephone
07850170612

Fax

Mobile

Work Email
paul.griffiths2@lthch.nhs.uk

Title Forename/Initials Surname
Dr Emanuele Giorgi

Post
MRC Fellowship in Biostatistics

Qualifications
BSc
PhD

Employer
Lancaster University

Work Address
CHICAS Lancaster Medical School
Lancaster University

Post Code
LA1 4YW

Telephone
07453286122

Fax

Mobile

Work Email
e.giorgi@lancaster.ac.uk

Title Forename/Initials Surname
Dr Sandra Oelbaum

Post
Clinical Director HealthAction

Qualifications
Medical Doctor

Employer
Health Action/Addaction

Work Address
67-69 Cowcross Street
London

Post Code
EC1M 6PU

Telephone
0782756488

Fax

Mobile

Work Email
sandra.oelbaum@addaction.org.uk

Title Forename/Initials Surname
Dr Sally Morrison

Post
Associate Medical Director

Qualifications
MBChB (Hons) MRCGP, MPhil, BSc (Hons)

Employer
Addaction

Work Address
67-69 Cowcross Street
A64. Lead Sponsor

Status:  ◯ NHS or HSC care organisation  
 ◯ Academic  
 ◯ Pharmaceutical industry  
 ◯ Medical device industry  
 ◯ Local Authority  
 ◯ Other social care provider (including voluntary sector or private organisation)  
 ◯ Other  

If Other, please specify:

Contact person

Name of organisation: Liverpool School of Tropical Medicine
Given name: Carl
Family name: Henry
Address: Liverpool School of Tropical Medicine, Pembroke Place
Town/city: Liverpool
Post code: L3 5QA
Country: UNITED KINGDOM
Telephone: 
Fax: 
E-mail: lstmrec@lstm.ac.uk

Is the sponsor based outside the UK?
◯ Yes  ◯ No

Under the Research Governance Framework for Health and Social Care, a sponsor outside the UK must appoint a legal representative established in the UK. Please consult the guidance notes.

A65. Has external funding for the research been secured?

Date: 18/09/2017
☑ Funding secured from one or more funders
☐ External funding application to one or more funders in progress
☐ No application for external funding will be made

What type of research project is this?
☐ Standalone project
☒ Project that is part of a programme grant
☐ Project that is part of a Centre grant
☐ Project that is part of a fellowship/ personal award/ research training award
☐ Other

Other – please state:

Please give details of funding applications.

<table>
<thead>
<tr>
<th>Organisation</th>
<th>MRC (As part of MRC DTP programme at LSTM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address</td>
<td>LSTM, Pembroke Place</td>
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<tr>
<td></td>
<td>Pembroke Place</td>
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<td></td>
<td>Liverpool</td>
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<td>Post Code</td>
<td>L3 5QA</td>
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<td>Telephone</td>
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<tr>
<td>Mobile</td>
<td>07980956309</td>
</tr>
<tr>
<td>Email</td>
<td><a href="mailto:kevin.mortimer@lstm.ac.uk">kevin.mortimer@lstm.ac.uk</a></td>
</tr>
</tbody>
</table>

Funding Application Status: ☑ Secured ☐ In progress

Amount: 5000

Duration

Years: 3
Months: 0

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?
This project is part of the LSTM MRC DTP PhD programme.

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1)? Please give details of subcontractors if applicable.

☐ Yes ☐ No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

☐ Yes ☐ No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the

Date: 18/09/2017
A69-1. How long do you expect the study to last in the UK?

Planned start date: 23/10/2017
Planned end date: 31/01/2019
Total duration:
Years: 1 Months: 3 Days: 9

A71-1. Is this study?

☐ Single centre
☐ Multicentre

A71-2. Where will the research take place? (Tick as appropriate)

☑ England
☐ Scotland
☐ Wales
☐ Northern Ireland
☐ Other countries in European Economic Area

Total UK sites in study 1

Does this trial involve countries outside the EU?

☐ Yes ☐ No

A72. Which organisations in the UK will host the research? Please indicate the type of organisation by ticking the box and give approximate numbers if known:

☐ NHS organisations in England
☐ NHS organisations in Wales
☐ NHS organisations in Scotland
☐ HSC organisations in Northern Ireland
☐ GP practices in England
☐ GP practices in Wales
☐ GP practices in Scotland
☐ GP practices in Northern Ireland
☐ Joint health and social care agencies (e.g. community mental health teams)
☐ Local authorities
☐ Phase 1 trial units
☐ Prison establishments
☐ Probation areas
☑ Independent (private or voluntary sector) organisations
☐ Educational establishments
☐ Independent research units
A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

☐ Yes  ☐ No

A76. Insurance/Indemnity—cover potential legal liabilities

[Note: In this section, NHS indemnity schemes include employers' schemes, professional indemnity schemes and insurance policies]

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? Please tick box(es) as applicable.

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

☐ NHS indemnity scheme will apply (NHS sponsors only)

☒ Other insurance or indemnity arrangements will apply (give details below)

Liverpool School of Tropical Medicine Insurance and Indemnity Scheme

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? Please tick box(es) as applicable.

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

☐ NHS indemnity scheme will apply (protocol authors with NHS contracts only)

☒ Other insurance or indemnity arrangements will apply (give details below)

Liverpool School of Tropical Medicine Insurance and Indemnity Scheme

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

☐ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)

☒ Research includes non-NHS sites (give details of insurance/indemnity arrangements for these sites below)

Liverpool School of Tropical Medicine Insurance and Indemnity Scheme

Date: 18/09/2017
Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

☐ Yes  ☐ No  ☐ Not sure
Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. For further information please refer to guidance.

<table>
<thead>
<tr>
<th>Investigator identifier</th>
<th>Research site</th>
<th>Investigator Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN1</td>
<td></td>
<td>Sally</td>
</tr>
<tr>
<td></td>
<td>NHS site</td>
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<tr>
<td></td>
<td>Non-NHS site</td>
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<tr>
<td>Institution name</td>
<td>Addaction</td>
<td></td>
</tr>
<tr>
<td>Department name</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Street address</td>
<td>67-69 Cowstreet</td>
<td></td>
</tr>
<tr>
<td>Town/city</td>
<td>London</td>
<td></td>
</tr>
<tr>
<td>Post Code</td>
<td>EC1M 6PU</td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>UNITED KINGDOM</td>
<td></td>
</tr>
<tr>
<td>Family name</td>
<td>Morrison</td>
<td></td>
</tr>
<tr>
<td>Forename</td>
<td></td>
<td></td>
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<tr>
<td>Middle name</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Email</td>
<td><a href="mailto:sally.morrison@addaction.org.uk">sally.morrison@addaction.org.uk</a></td>
<td></td>
</tr>
<tr>
<td>Qualification (MD...)</td>
<td>MBChB (Hons) MRCGP MPhil BSc (Hons)</td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>UNITED KINGDOM</td>
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</tbody>
</table>
D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.

9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:
   - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
   - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
   - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
   - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
   - May be sent by email to REC members.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

11. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee’s final opinion or the withdrawal of the application.

Contact point for publication (Not applicable for R&D Forms)
NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

☒ Chief Investigator

Date: 18/09/2017
Access to application for training purposes (Not applicable for R&D Forms)
Optional – please tick as appropriate:

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Mrs Rebecca Nightingale on 18/09/2017 10:34.

Job Title/Post: PhD student
Organisation: Liverpool School of Tropical Medicine
Email: rebecca.nightingale@lstmed.ac.uk

[Signature]

Liverpool School of Tropical Medicine

HASSAN BURMAN

hassan.burman@rbht.nhs.uk
D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co-sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

   Please note: The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.

6. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

7. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Mr Carl Henry on 18/09/2017 10:50.

Job Title/Post: Research Governance Manager

Organisation: Liverpool School of Tropical Medicine

Email: lstmgov@lstmed.ac.uk
D3. Declaration for student projects by academic supervisor(s)

1. I have read and approved both the research proposal and this application. I am satisfied that the scientific content of the research is satisfactory for an educational qualification at this level.

2. I undertake to fulfill the responsibilities of the supervisor for this study as set out in the Research Governance Framework for Health and Social Care.

3. I take responsibility for ensuring that this study is conducted in accordance with the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research, in conjunction with clinical supervisors as appropriate.

4. I take responsibility for ensuring that the applicant is up to date and complies with the requirements of the law and relevant guidelines relating to security and confidentiality of patient and other personal data, in conjunction with clinical supervisors as appropriate.

<table>
<thead>
<tr>
<th>Academic supervisor 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>This section was signed electronically by Dr Kevin Mortimer on 18/09/2017 10:36.</td>
</tr>
<tr>
<td>Job Title/Post:</td>
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<tr>
<td>Organisation:</td>
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<td>Email:</td>
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</table>

<table>
<thead>
<tr>
<th>Academic supervisor 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>This section was signed electronically by Dr Jamie Rylance on 18/09/2017 10:46.</td>
</tr>
<tr>
<td>Job Title/Post: Senior Clinical Lecturer</td>
</tr>
<tr>
<td>Organisation: Liverpool School of Tropical Medicine</td>
</tr>
<tr>
<td>Email: <a href="mailto:jamie.rylance@lstmed.ac.uk">jamie.rylance@lstmed.ac.uk</a></td>
</tr>
</tbody>
</table>
Section 4: Patient Information Sheet

A Study to ascertain the severity and nature of COPD at a drug dependence clinic

Participant Information Sheet

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Designation</th>
<th>Contact telephone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebecca Nightingale</td>
<td>PhD Student</td>
<td>07379917339</td>
</tr>
<tr>
<td>Dr Hassan Burhan</td>
<td>Consultant Physician</td>
<td>0151 7063306</td>
</tr>
<tr>
<td>Dr Paul Griffiths</td>
<td>Respiratory Registrar</td>
<td>0151 6001153</td>
</tr>
</tbody>
</table>

You are being invited to take part in a research study involving Liverpool School of Tropical Medicine and Addaction. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

This leaflet gives you detailed information about the purpose and conduct of this study and what will happen to you if you take part.

Ask us if there is anything that is not clear or if you would like more information in order to decide whether or not you wish to take part.

What is the purpose of the study?

We recognise that it can sometimes be hard to attend appointments at the GP or in hospital to discuss health problems and to have investigations. We suspect you may have problems with your chest/lungs, particularly if you are, or have been, a smoker. With just a few questions and simple tests we can find out more about your lungs and how they have changed since last time you did these tests at Addaction. It may be that you have asthma or Chronic Obstructive Pulmonary Disease (COPD) which are both diseases in which airways in the lungs become narrower and make it hard for air to get in and out of the lungs. We would like to know if this is effecting you and how we could make treatment improvements for you.

What is involved?

We are recruiting patients to this study in order to investigate whether people seen at the drug dependence clinic have previously undiagnosed chest problems.

Who should take part?

Anyone seen at the drug dependence clinic run by Addaction and had previous spirometry in this clinic may take part.
Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the care you receive.

What do I have to do?

After giving you time to read through the information, a member of the study team will ask your decision. If you agree to take part you will be asked to sign a consent form. You may chose to take part in either the questionnaire part or the breathing test part, or both.

During your visit to see your key-worker or doctor at the clinic you will be interviewed by a member of the research team, who will go through a short questionnaire with you. They will ask you questions about your chest, about the amount of tobacco and/or drugs you have smoked in the past and about any inhalers you may take. The answers to these questions will only be seen by the research team, your Addaction doctor and if you consent your GP.

If you agree the research team will look at your previous breathing test results and medical records (hospital/ GP and Addaction) to see what problems you have had with your chest and if your treatment has changed. We would also like to know how often you have seen your GP or been to hospital because of your chest. how many times you have attended different health care facilities. No unnecessary medical details will be recorded and data will be anonymised once collected.

You will also be asked to do a breathing test called spirometry. Spirometry is a test that can help diagnose various lung conditions and measures the amount of air that you can blow out and how fast. You breathe in fully and then blow out as fast and as much as you can until your lungs are completely empty. This will take a few seconds. A clip may be put on your nose to make sure that no air escapes from your nose. The test will be done at least 3 times over a few minutes and occasionally more. If you have not used an inhaler in the 6 hours before the test, we will get you to use a blue inhaler to try to open up the airways and then we will repeat the test. You should not take part in spirometry if you have recently had a collapsed lung, heart or chest surgery, a blood clot in your leg or lung or coughed up blood, had a recent heart attack or stroke, have a severe ear infection or are been treated for TB. If you believe you have any of these please inform the researcher but you may still be able to complete questionnaire.

You may be asked if you would like participate in a longer interview where you can tell us your views and opinions about the care you get for your chest.

Do any blood samples need to be collected?

No.

What are the benefits of taking part?
If a chest problem is suspected or diagnosed as a result of the questionnaire and blowing tests your GP will be able to further assess you, possibly arrange further tests or giving you treatment. Having blowing tests done as part of the study may avoid you having to make an appointment to have these done at another time. Earlier treatment of lung disease can help to reduce the risk of illness, future breathlessness, chest infection, need to see a GP or attend hospital. By improving physical health potentially it can also help you to reduce cigarette and drug use.

**What are the risks?**

Every effort will be made to minimise the risk of harm to participating patients and there is very little risk involved in this study. Spirometry is a very simple test performed thousands and thousands of times each year in the UK. Blowing out hard can sometimes temporarily increase the pressure in your chest, abdomen or eyes. This can lead to ‘watery’ eyes or wheezing or mild, temporary breathlessness.

**What if I change my mind?**

Your involvement in this research is voluntary. By reading this patient information sheet you are not in any way obliged to take part. You have the right to change your mind, or withdraw your consent, at any time during the study, without giving reasons. This will have no effect on your future care within the NHS or your medical or legal rights. You will be removed from the study immediately. All data collected up to that point will be retained by the study team.

**What if I wish to complain about the way in which this study has been conducted?**

If you have any cause to complain about any aspect of the way in which you have been approached or treated during the course of this study, the normal NHS complaints mechanisms are available to you and are not compromised in any way because you have taken part in a research study. If you have any complaints or concerns please contact the Customer Service Team (formerly known as PALS) in your hospital. You may also complain via the Addaction local complaints service or via your keyworker.

**Will my details be kept confidential?**

Yes. Members of Addaction and the named research team will have access to your questionnaire and spirometry data plus your GP if you give us permission to tell him or her. Other members will only have access to anonymised data.

We will ask your permission to inform your GP that you are taking part in the study as this may be relevant to your medical care outside the study. Any information of value to your care will be conveyed to you and to your doctors.

All information we collect will be kept secure and confidential. Your research notes will be kept separate from your NHS notes. All data will be collected and stored within the Liverpool School of Tropical Medicine. It will be stored for a period of 7 years after publication (or longer if required by a publishing journal). No publication or presentation regarding this study will contain information that can identify any particular volunteer.
Further questions?

If you have any further questions about this study please contact:

• Rebecca Nightingale 07379917339
• Dr Hassan Burhan 0151 7063306

You will be given a copy of this information sheet and of your signed consent form to keep.

Thank you.
Appendix for Chapter Three

Section 1: PDF of Paper
Exploring perspectives on chronic obstructive pulmonary disease in people who smoke heroin: a qualitative study

Rebecca Nightingale1,2,3*, Paul Griffiths2, Kevin Mortimer1, Paul Walker4, Tara Byrne5, Kerry Marwood5, Sally Morrison-Griffiths5, Sue Renwick6, Jamie Rylance1,3†, Hassan Burhan2†

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Abstract

Background: Smoking rather than injecting heroin has become more common over the last 20 years. Although there is an increasing body of evidence describing high levels of chronic obstructive pulmonary disease (COPD) in people who smoke heroin, there is limited evidence documenting the impact of the long-term condition on this population group.

Aim: This study aimed to describe the experiences of people who smoke heroin with COPD in Liverpool, UK.

Design & setting: Participants were purposefully sampled for this qualitative study. They included adults enrolled in an opioid replacement clinic run by Addaction in Liverpool, who had already engaged with spirometry testing for COPD as part of a previous study.

Method: Semi-structured interviews were performed with participants with spirometrically confirmed COPD in opioid replacement clinics. Data were analysed using a framework analysis approach.

Results: Sixteen potential participants were invited to take part in the study, of which 10 agreed and were interviewed. Three themes common to all interviews were identified: functional measures of lung health that impacted on their activities of daily living; inhaler and medication perceptions with erratic use that was not concordant with their prescription; and the impact of difficulties accessing care.

Conclusion: These findings, along with previous studies highlighting the prevalence of COPD in this population, warrant efforts to integrate community COPD and opioid replacement services to improve outcomes for this vulnerable population.

How this fits in

There is a growing body of evidence of high levels of COPD in people who smoke heroin. This appears to happen at an earlier age than the general population. This qualitative study investigates the experiences of these patients and provides clinicians with new insights into the challenges facing this population. These results can be used to help guide the planning of future primary care services for this group of patients.

Introduction

Over the last two decades, people who use heroin have increasingly smoked rather than injected the drug, understanding this to be a method of harm reduction.1,2 This has, however, led many people...
who smoke heroin to develop COPD at an earlier age than typically seen in those who exclusively smoke tobacco. A recent study in Liverpool demonstrated that approximately 50% of people who smoke heroin have COPD or its overlap syndrome with asthma. Those with COPD reported extensive respiratory symptoms, such as shortness of breath, cough, and wheeze, which are likely to lead to increased hospital admissions. Screening people who use heroin for COPD may be an important part of providing care early in the course of the disease and limiting the burden of acute hospital care.

There is limited evidence regarding patient experience among people who use heroin. The study, therefore, sought insight into the experience and challenges faced by people who smoke heroin with COPD in order to shape future screening and treatment services. This qualitative study examined the lived experience of those with symptoms and a diagnosis of chronic lung disease, and of their experience of interfacing with healthcare services to access treatment.

Method

Semi-structured interviews were conducted with people who smoke heroin diagnosed with COPD as part of a screening programme between December 2017 and April 2018.

Study context

The interviews were carried out in Addaction community opioid replacement clinics in Liverpool as part of a COPD screening programme. Addaction is a large independent charity commissioned by the local city council public health department. The screening programme has been previously reported. Between December 2015 and June 2016, participants had been evaluated using respiratory symptom-specific questionnaires, and spirometry to test their lung function. Follow-up screening took place between December 2017 and April 2018.

Recruitment

Within Addaction clinics for opioid replacement therapy, key workers were asked to identify potential participants for the qualitative study. All had been diagnosed with COPD during baseline screening and were current or previous smokers of heroin. Potential participants were given study information prior to their appointment and if they agreed to being interviewed, a key worker who knew them notified the study team. The key worker was not present during the interviews, but was available for support as necessary. Written informed consent was obtained from all participants.

Data collection

Interviews were led by a researcher (PG) independent of the quantitative screening study, with experience of qualitative research and extensive medical knowledge of COPD. The researcher was aware the participant had COPD but knew no further clinical details. The interviews took place within the two large Addaction clinic sites in Liverpool, in rooms separate from the clinics to remove the participants from the clinical environment, and with refreshments provided. The researcher followed the topic guide, which included: reported symptoms or problems; understanding of COPD; understanding of medications; and experience of access to care. Open questions were asked, with pre-prepared probing questions to gain further information (see Supplementary Appendix S1). All interviews were digitally recorded and identified by participant number only.

Analysis

A framework analysis approach was used, taking five steps to results: familiarisation; coding; developing and applying a framework; charting; and interpretation. Each interview was transcribed verbatim, and the transcripts were read through by two researchers (RN and PG) for familiarisation. Following this, RN and PG agreed on the major coded themes based on the topic guide. The data were coded separately in Microsoft Excel, with the transcripts colour-coded for each theme in Microsoft Word. These codes were then shared with the wider research team (RN, PG, JR, HB) and a thematic framework was developed through discussion until a consensus was reached on the mapping of the codes. The themes were shared with Addaction staff members who were part of the research team to ensure they were accurate to the setting and true to the original topic guides (TB and KM).
Results
Sixteen potential participants were invited, 10 of whom agreed to take part and were interviewed. The age range of those interviewed was 47–59 years, with eight males and two females taking part; all were white. The participants had a range of COPD severity measured by the Global Initiative for Obstructive Lung Disease classifications (mild $n=4$, moderate $n=3$, severe $n=3$). All were taking opioid replacement therapy, with seven reporting they still smoke heroin. Following the interview framework, three themes common to all interviews were identified: functional measures of lung health that impacted on their activities of daily living; inhaler and medication perceptions with erratic use that was not concordant with their prescription; and the impact of difficulties accessing care.

Functional measures of lung health
All participants described their COPD in relation to the degree of functional limitation imposed by their symptoms. None of the participants described their COPD or lung disease in terms of medical outcomes such as spirometry results or breathlessness scores. Every participant had concerns about how COPD was affecting their everyday activities of daily life:

‘You know every day I get up in the morning, I go to make a cup of coffee and I come back in and sit down and I’m gasping for breath and I can’t catch my breath, I just can’t get it, you know what I mean?’ (Interview 5)

‘I mean I often don’t go out, I struggle carrying shopping, I use one of them now, a bag over your shoulder, with the string, they help me to walk, a lot better. One time, I was putting the bags down, walk a bit, get my breath, again and again, oh God, it was horrendous.’ (Interview 10)

Participants described how their functional capacity had deteriorated over time. Eight participants recognised a worsening over a period of months or years. COPD was not explicitly mentioned in these cases, rather the participants described problems with their ‘lungs’ or ‘chest’ but did not necessarily attribute their problems to, or label their condition as, COPD:

‘I was just speedy me. I was just one of them people, but now, now I just can’t even, even when my son was 7, I mean he’s 15 now, I was still doing the garden but I couldn’t breathe. I’ve stopped trying to do the garden I mean coz that nearly killed me, I mean it, bad palpitations, I think it would have killed me that day, my neighbour came out and said “go in, get in now!” and stayed with me and everything.’ (Interview 9)

‘I can’t any more, I was quite active say 10 years ago, but now I can’t run, can go slow on a bike but that’s it, couldn’t run if I wanted to … yeah, just from walking, or as I’ve said just getting out of bed, I can walk to the landing to look out the window and be standing panting, thinking “where’s the inhalers” and it’s only when I have the inhalers that it seems to calm me down a bit.’ (Interview 3)

Two participants did not perceive their chest to be a significant problem; both described functional limitation, but reported it as normal for them:

‘I did run for the bus the other day and feel a bit out of breath, but most people wouldn’t they? Running for the bus and exerting yourselves, you know, at 8 o’clock in the morning … I’ve got to be very fit and active every single day … So my chest isn’t too bad considering what I’ve put into it over the years, at least from my perspective it’s not.’ (Interview 2)

‘No … no it doesn’t stop me, and the inhalers I don’t use them every day, only when I need to, only when I’m coughing and short of breath I’ll use them then … yeah but only when I’m coughing, sometimes I cough and I’m nearly puking … maybe two or three times a week.’ (Interview 4)

Inhalers and medication perceptions
All participants reported taking at least one inhaler and talked about them consistently during the interviews. Of the 10 participants interviewed, seven reported that they had recently borrowed other
people’s inhalers or medication to help their chest. The reasons for this were not always identifiable, but access to medication was a frequent difficulty:

‘... well the last one I needed I got off my cousin coz she had a spare.’ (Interview 4)

‘My girlfriend has one of those nebuliser things so I just throw myself on that, and erm, that kind of makes me feel ok.’ (Interview 6)

‘If there’s antibiotics in the house then I’ll use them instead [of going to a doctor] … it’s like, I’ve been around drugs most of my life, so I’m not afraid to try an antibiotic or something if I think it might help me … well the wife has got asthma there, so err she got inhalers, a brown one and a blue one, and I’ll use them every now and again … They’ve told me COPD is different to asthma so instead of using the wife’s stuff, I might need something else, a different one for my condition might be better.’ (Interview 7)

Participants also reported the use of metered-dose inhalers (MDIs) as drug pipes, either by themselves or others:

‘We used to make bongs out them, the blue one [salbutamol MDI], years ago, but God I couldn’t even look at doing that now it knocks me sick.’ (Interview 9)

‘You just [describes process of converting inhaler into a drug pipe] ... Yeah yeah the blue ones, the hollow tube […] I’ve seen a lot of people use them like that, like “rock pipes” we called them ... So it’s a common thing to do ... It sounds mad that people are using things meant to help you breathe for that stuff doesn’t it?’ (Interview 4)

There was generally poor knowledge and understanding surrounding inhalers, with participants confused between the name of the inhaler and the colour; for example, describing a ‘blue inhaler’ but pointing to a purple (Seretide) inhaler (interview 1). In general, participants described high usage of the ‘blue inhaler’ (salbutamol) and inconsistent use of long-acting medication such as tiotropium or formoterol. Participants reported that they used inhalers as and when they needed them, and there appeared to be a lack of understanding of using longer-term inhalers as prevention for some of the functional problems they described:

‘I use the inhalers carefully, don’t waste them you know, use them as and when I feel I really need them, I don’t use them for the fun of it, I’ll only use them when I feel as though I’m struggling.’ (Interview 8)

‘Talking about the “blue and pink”? Nah I don’t use any of them regularly, only when I get bouts of it.’ (Interview 4)

Impact of access to care

The difficulty in accessing both primary care appointments and hospital appointments was a recurring theme. The participants described travel to and from appointments as a barrier to attending both the GP surgery and the hospital. In some circumstances the cost of travel was prohibitive and in others it was the practicalities of getting out of the house while being unwell. The participants suggested that they may attend more often if access to care was easier:

‘... well it’s two buses away, and it kills me to get there, but I love that doctor so I make the effort if I need to.’ (Interview 1)

‘It can be a bit of a task though, with the breathing and that, sometimes I only have to walk around the corner and I’m having a bad time ... yeah well I have to walk here as well so that can be hard in itself, stop and rest about 20 times ... you’d see me sat down on the road and all that, you know what I mean?’ (Interview 6)

‘I just can’t get there, even if I phone a taxi to come and take me, I just can’t get up and down the stairs.’ (Interview 8)

The experience that participants had of their GPs and hospital doctors varied throughout the interviews, with participants describing their GP as ‘marvellous’ (interview 1) and saying ‘I can’t fault him’ (interview 10). All participants reported that seeing their own GP was difficult; either they saw a
locum, which they reported as a negative experience, or that getting an appointment via reception was difficult:

‘... well it’s hard to get an appointment at the doctors, to get my script, and God did I feel it when I ran out, really bad.’ (Interview 1)

‘... you know the credit on your phone to ring up, and you know when they say to ring at 8 o’clock in the morning, well try using somebody else’s phone, like I’ve had to use before, at eight in the morning. That’s no good to me.’ (Interview 10)

‘... maybe receptionists, when you phone up you’ve got to phone at certain times, waiting to get through to the receptionists, you see it’s like you wait for the phones to turn over at 8:20am and you might not get through ’til 9:20am and they’ve all gone, so, that’s not good ... like I could have a problem like today, and I’ll go in or ring up and they’ll say “yeah we can fit you in in 2 weeks’ time”, well hang on, you know?’ (Interview 8)

The participants generally reported that they did not attend hospital appointments. There were a variety of reasons for this, including the feeling of stigma or that chest problems were ‘self-inflicted’. Several participants avoided secondary care environments owing to negative associations with, for example, a dying relative, or a negative experience with the hospital staff:

‘I think they’re rushed off their feet, so you know, I think there’s sicker people than me to be seen to ... coz mine are self-inflicted, like they see sick children and it just shows you that I’ve done this to myself, you know? ... because it’s self-inflicted isn’t it? I just feel embarrassed wasting the national health money ... ’ (Interview 1)

‘... well they can’t do nothing can they, the doctors can’t do nothing for my chest the way it is, I have inhalers, I asked them about nebulisers, they said I don’t need a nebuliser, so, but I think I do like ... I don’t know, I feel like they just look at you and think ”ah its self-inflicted” and that ...

'[when admitted with chest problem] I’m on certain medication that they just won’t give you, like the methadone, they just won’t give you that, so I’ve got to lie there, like if I go in on a Friday I’ve got to lie there until Monday, with no nothin’. So you’re in bits by Monday, they sort your dose out, I know people might try and cheat the system, but you know, it goes on, I’m not going to abuse it and as doctors and nurses you’ve got to think “is this man on this?”. For one time in the hospital I was on 360 ml a day, so when the doctors read that they thought ”F*ck off no way”, you’d say as well. I mean I’m not on that now. They say to you get a stat dose of 20 ml, but what that’s gonna do for me when I’m on 360? It doesn’t help. It’s experiences like that, the last thing I’d want to do is ring an ambulance if I can help it.’ (Interview 8)

Discussion

Summary
Using qualitative interviews, this study has shown the key challenges for this cohort are lung health symptoms that impacted on their activities of daily living; inhaler and medication perceptions, with erratic use that was not concordant with their prescription; and the impacts of difficulties accessing care. These themes occurred throughout the interviews and could help inform and develop respiratory services for this group of patients.

Strengths and limitations
The main limitation of this study is the small number of interviews conducted and the breadth of the interviews conducted. It may have added to the depth of knowledge if healthcare providers had also been interviewed, and further study in this area would be informative. The participants who declined to take part may have led to bias, with those happier to engage or those with strong opinions about their COPD potentially more likely to take part. This study has, however, offered a new and unique view on the possible barriers facing people with COPD who smoke heroin.
Comparison with existing literature

The participants’ main focus was the functional limitation that they experienced in their activities of daily living as a result of their COPD. No participant discussed the details of their medical diagnosis, the staging of their COPD or used medical scoring, such as MRC (Medical Research Council) and COPD assessment test (CAT), to describe their COPD. To the best of the authors’ knowledge, there are no studies that specifically describe the impact and functional limitations of COPD in people who smoke heroin; however, the themes identified in this study are similar to studies of people who smoke tobacco. In a large pan-European study examining patients with COPD and their experience of acute exacerbations, there was wide variability in reported symptoms between patients (reported at 62.7%), high levels of self-medication, and poor understanding of their condition. The impact of COPD-related symptoms on activities of daily living has been evaluated previously, with there being a high prevalence of impaired functioning among patients with COPD across a wide range of domains. The impairment does not clearly correlate with standard clinical measures such as degree of airflow obstruction or level of dyspnoea. Furthermore, functional limitation was common among the participants in the study and was often deemed to be ‘normal’ by individuals. Relying on objective measures of COPD severity in this patient population may not identify individuals who would benefit from more targeted interventions, such as pulmonary rehabilitation, aiming to improve symptoms and level of functioning with regards to activities of daily living.

In general, the study participants appeared to be taking COPD medication in an irregular and often self-directed manner. In some, inhalers were used as a vehicle for smoking drugs rather than for their intended purpose. The engagement with the primary care system in the UK was mixed, with some participants having an excellent experience of their GP, while others found significant barriers to attending primary care, with travel and access to the GP being the principle negative factors. Participants universally found accessing hospital treatment difficult, with stigma and a feeling of having a ‘self-inflicted’ illness limiting attendance at the hospital.

Poor adherence and a lack of knowledge or trust in medication has been reported in other studies of COPD patients, with overuse, underuse, and alteration from medication schedule commonplace. In a cross-sectional study of 173 patients with COPD attending outpatient clinics, 29.5% of attendees had ‘low adherence’ to medication. The theme of accessing prescription medication from peers or family members is also not unique to the study population, with another study on students finding that those who access medication from peers were also more likely to use illicit drugs. Stigma and significant barriers to accessing both primary and secondary care are common across illicit drug users, with reports of ‘dissonant care’ commonplace with other qualitative and narrative studies in this population, describing similar findings to the analysis of the interviews in the present study.

Implications for research and practice

The data highlight important considerations in the development of COPD services for drugs users. Clinicians should consider functional outcomes as well as clinical outcomes and objective scoring systems when discussing COPD treatment with patients. There is potential that functional goals would be welcomed by this patient group and may help motivate the attendance to care and adherence to treatment. The use of self-medicated inhalers, nebulisers, and other drugs makes clinical assessment even more challenging in this population. It is highly likely that the standard methods of assessing ‘medication pick-up’ at pharmacies does not provide an accurate picture, and that self-reported usage may be key to determining the real clinical need. Alongside this, the overuse of some inhalers, potentially as drug paraphernalia, adds to an already complex clinical picture. The access to respiratory care for this patient group is limited, with barriers including transport to hospitals and a feeling of stigma. There is potential that providing respiratory care centred around venues where patients attend opioid replacement therapy would improve continuity of care and assist in obtaining accurate medication histories. This research highlights the complex needs of people who smoke heroin with COPD and the need to consider their functional limitations, medication management, and access to care in future planning of respiratory services.

Funding

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interviews.

**Ethical approval**
Ethical approval was gained from Health Research Authority (HRA) via the integrated Research Application System (IRAS) (reference number: 235,151).

**Provenance**
Freely submitted; externally peer reviewed.

**References**


Section 2: Supplement to Paper


Individual interviews

Introduction

Good Morning. My name is………………Thank you for coming, to this interview, I will ask you a few questions about your views of your chest condition, feel free to talk openly to me, all information is confidential. If you do not want to answer a question then that is fine, it will not effect your participation in the study or any of your care. I will record the interview so I don’t miss anything, this interview will last approximately 30-45 minutes.

Purpose

The purpose is find out if you feel your chest/respiratory condition, how you feel about the care that you receive and what are your views and experiences of using inhalers. There are no wrong or right answers; these are your opinions and your personal experiences.

Interview

Do you feel that you have any problems with your chest or breathing?

Probes: Have you ever been told you have a problem with your chest?

Who have you sought help from?

Probes: Have they been to the GP? If so, what was the experience like? If not attended, why?

Have you ever attended an Accident and Emergency (A&E) department due to chest problems?

Probes: If so, what was the experience like?

What do you feel could be done differently to make your treatment work better for you?

Probes: Is it easy to get an appointment with your care provider? Does the timing and venue of this appointment work for you? How are you treated by the healthcare provider/s?

Have you been given inhalers for your chest problem? What is your experience of getting medication?

Probes: Do you find it hard to get to repeat prescriptions/access to your GP? Is your GP happy to prescribe your regular medications?

How do you use your inhalers?

Probes: Do you take them regularly? Have you been taught how to take them? Do you use them for anything else? Can they describe the technique?

Closure

Thank you for participating in this interview. Is there anything else you would like to add to the conversation? This has been very helpful and I appreciate your time.

For Ethics and Patient information sheets please see appendix one
Appendix for Chapter Four

Section 1: PDF of Paper
Noncommunicable Respiratory Disease and Air Pollution Exposure in Malawi (CAPS): A Cross-Sectional Study

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Abstract

Rationale: Noncommunicable respiratory diseases and exposure to air pollution are thought to be important contributors to morbidity and mortality in sub-Saharan African adults.

Objectives: We set out to explore the prevalence and determinants of noncommunicable respiratory disease among adults living in Chikhwawa District, Malawi.

Methods: We performed a cross-sectional study among adults in communities participating in a randomized controlled trial of a cleaner-burning biomass-fueled cookstove intervention (CAPS [Cooking and Pneumonia Study]) in rural Malawi. We assessed chronic respiratory symptoms, spirometric abnormalities, and personal exposure to air pollution (particulate matter <2.5 μm in aerodynamic diameter [PM2.5] and carbon monoxide [CO]). Weighted prevalence estimates were calculated; multivariable and intention-to-treat analyses were done.

Measurements and Main Results: One thousand four hundred eighty-one participants (mean [SD] age, 43.8 [17.8] yr; 57% female) were recruited. The prevalence of chronic respiratory symptoms, spirometric obstruction, and restriction were 13.6% (95% confidence interval [CI], 11.9–15.4), 8.7% (95% CI, 7.0–10.7), and 34.8% (95% CI, 31.7–38.0), respectively. Median 48-hour personal PM2.5 and CO exposures were 71.0 μg/m3 (interquartile range [IQR], 44.6–119.2) and 1.23 ppm (IQR, 0.79–1.93), respectively. Chronic respiratory symptoms were associated with current/ex-smoking (odds ratio [OR], 1.59; 95% CI, 1.05–2.39), previous tuberculosis (OR, 2.50; 95% CI, 1.04–5.18), and CO exposure (OR, 1.46; 95% CI, 1.04–2.05). Exposure to PM2.5 was not associated with any demographic, clinical, or spirometric characteristics. There was no effect of the CAPS intervention on any of the secondary trial outcomes.

Conclusions: The burden of chronic respiratory symptoms, abnormal spirometry, and air pollution exposures in adults in rural Malawi is of considerable potential public health importance. We found little evidence that air pollution exposures were associated with chronic respiratory symptoms or spirometric abnormalities and no evidence that the CAPS intervention had effects on the secondary trial outcomes. More effective prevention and control strategies for noncommunicable respiratory disease in sub-Saharan Africa are needed.

Clinical trial registered with www.isrctn.com (ISRCTN 59448623).

Keywords: household air pollution; Malawi; chronic obstructive pulmonary disease; Cooking and Pneumonia Study; cookstove

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‡Co–senior authors.
§J.B. is Associate Editor of AJRCCM. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

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This article has an online supplement, which is accessible from this issue’s table of contents at www.atsjournals.org.

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At a Glance Commentary

Scientific Knowledge on the Subject: Noncommunicable respiratory diseases and exposure to air pollution are thought to be important causes of morbidity and mortality in sub-Saharan African adults. Recent BOLD (Burden of Obstructive Lung Disease) studies found a high burden of spirometric restriction but little spirometric obstruction in several sub-Saharan African countries and no association between spirometric obstruction and use of dirty-burning fuels. It is not known whether an association between spirometric obstruction and solid fuel use would be seen if personal exposure to air pollution were measured in addition to self-reported exposure. CAPS (Cooking and Pneumonia Study)—a trial of cleaner burning biomass-fueled cookstoves on pneumonia in children <5 years of age in rural Malawi—offered the opportunity to explore this and other secondary trial outcomes in adults.

What This Study Adds to the Field: In adults living in Chikhwawa, rural Malawi: 13.6% of participants had chronic respiratory symptoms (mainly cough); >40% had abnormal spirometry (mainly spirometric restriction); day-to-day air pollution exposures were approximately three times the World Health Organization upper safety limit; air pollution exposures were not associated with demographic, clinical, or spirometric characteristics; and there was no association between CAPS trial arm and any of the secondary trial outcomes.

Highly polluting fuels, including animal dung, crop residues, wood, charcoal, and kerosene, are used by almost half the world’s population to provide energy for cooking, heating, and lighting (1–3). These fuels are typically burned in and around the home environment in inefficient ways (e.g., open fires), which leads to high levels of air pollution in and immediately outside of homes. The World Health Organization (WHO) has estimated that exposure to household air pollution leads to >4 million deaths each year (3). The latest Global Burden of Disease Study estimates this number is closer to 2.5 million, but even these lower estimates represent a substantial burden of morbidity and mortality that falls particularly heavily on the world’s poor (4).

Household air pollution has been considered to increase the risk of pneumonia in children and of chronic obstructive pulmonary disease (COPD) and cardiovascular disease in adults (1–3).

In 2017, we published the findings of a cluster-randomized controlled trial of introducing a cleaner-burning biomass-fueled cookstove to prevent pneumonia in children <5 years of age in rural Malawi (CAPS [Cooking and Pneumonia Study]) (5). CAPS is one of a small number of trials done to date to evaluate the effects of reducing biomass smoke exposure on health outcomes and is the largest trial of a cookstove intervention on health outcomes conducted anywhere in the world (n = 10,750 children from 8,626 households across 150 clusters). The major finding of this trial was that there was no difference between the intervention and control groups among children in pneumonia incidence defined using the criteria of the Integrated Management of Childhood Illness program. This unexpected finding has cast some doubt on the assumptions made by the Global Alliance for Clean Cookstoves that cleaner cookstoves and fuels save lives (6–11).

Herein we report the findings of a cross-sectional study of the prevalence and determinants of noncommunicable respiratory disease among adults living in communities that participated in CAPS, which addresses the prespecified secondary trial objective of determining prevalence and determinants of obstructive lung disease in adults in rural Malawi (5). In this setting, use of highly polluting fuels for day-to-day household energy requirements is the norm, and therefore a high burden of COPD associated with household air pollution was expected.

Methods

Study Design
We performed a cross-sectional study of the prevalence and determinants of noncommunicable respiratory disease among adults living in Chikhwawa District, Malawi.

Setting
Chikhwawa is ~50 km from the nearest city, Blantyre, on the southern Shire River Valley, and it consists primarily of subsistence farmers living in rural village communities. The Malawi College of Medicine Research Ethics Committee (Ethics Committee reference no. P.11/12/1308) and the Liverpool School of Tropical Medicine Research Ethics Committee (Ethics Committee reference no. 12.40) approved the CAPS trial protocol that includes this work, a summary of which was published by The Lancet (12).

Participants
Following community engagement events that included village leaders and other community representatives, a list of all the adults living in each of the 50 villages participating in CAPS in Chikhwawa was obtained from local community health workers known as Health Surveillance Assistants. These lists were collated and used by an independent statistician at the BOLD (Burden of Obstructive Lung Disease) center in London to obtain a population-representative sample of adults >18 years of age with stratification by age and sex. All potential participants sampled in this way were then individually invited to participate with written informed consent (or witnesses thumbprint for those unable to read and write) obtained from those who agreed.

People who were acutely unwell, not

Author Contributions: Design: K.M., P.B., and J.B. Acquisition of data: R.N., K.M., P.B., and J.B. Analysis of data: R.N., M.L., G.F., and S.J.R. Interpretation of data: R.N., M.L., G.F., S.J.R., J.M., P.B., J.B., and K.M. Writing the manuscript, approval of the version to be published, and agreement to be accountable for all aspects of the work: all authors.

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permanent residents, or pregnant were excluded.

**Procedures**

Fieldworkers who had undergone study-specific training and met the required quality standards did home visits according to standardized operating procedures. With the exception of the air pollution monitoring procedures that are not part of the BOLD study protocol, all procedures were conducted in accordance with the BOLD study protocol, which has been described previously (13). Minimal demographic information was collected from participants who declined to participate in the full study. Fieldworkers administered BOLD study questionnaires in the local language, Chichewa. Height and weight were measured using a portable stadiometer and scales. All eligible participants were asked to do before and after bronchodilator spirometry, which BOLD center-certified fieldworkers performed to European Respiratory Society/American Thoracic Society guidelines using the ndd EasyOne spirometer (ndd Medical Technologies) (14). Up to three repeat visits were arranged to achieve the required spirometry quality standards. Spirometry data were sent electronically to the BOLD center for quality control.

Personal exposures to particulate matter <2.5 μm in aerodynamic diameter (PM$_{2.5}$) and carbon monoxide (CO) were measured continuously for 48 hours using the indoor air pollution (IAP) 5000 series monitor (Aprovecho Research Center). The IAP 5000 sampled air from the breathing zone using a short tube and logged continuous PM$_{2.5}$ and CO using a light-scattering photometer and an electrochemical cell CO sensor, respectively. All monitors were calibrated at the Aprovecho Research Center prior to use in the study. Monitors were worn in small backpacks apart from during sleep, when they were kept beside the sleeping mat or bed.

**Variables**

Clinical outcomes were presence or absence of specific symptoms as assessed by a questionnaire. The questions (outcomes) asked were as follows: Do you usually have a cough when you don’t have a cold (cough outcome)? Do you usually bring up phlegm from your chest (phlegm outcome)? Have you had wheezing/whistling in your chest at any point in the last 12 months, in the absence of a cold (wheeze outcome)? Do you have shortness of breath when hurrying on the level or walking up a slight hill (dyspnea outcome)? And have your breathing problems interfered with your daily activities (functional limitation outcome)? A composite variable for any symptoms was created by defining as positive if an individual reported any of the above symptoms (any symptoms outcome).

Continuous FEV$_1$ and FVC spirometry values were used in the primary analysis. Spirometric obstruction and restriction were defined according to the NHANES III white reference range lower limits of normal (15).

Exposures of interest included personal exposure to PM$_{2.5}$ or CO as measured by the personal monitoring device, and two exposures assessed by questionnaire: smoking status and previous episode of tuberculosis (TB). A questionnaire-assessed variable asking for any biomass exposure was considered, but as most (>99%) indicated yes, it was not included in any modeling.

Raw PM$_{2.5}$ and CO exposures were corrected for background levels using

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**Figure 1.** Participant recruitment flow diagram. TB = tuberculosis.
calibration values for each monitoring period. In cases where calibration data were missing or corrupted (<5%), aggregated mean calibration values were used. Observations where <2,000 minutes of time were recorded were excluded, as were monitoring periods affected by device malfunction. Both PM$_{2.5}$ and CO were log$_{10}$ transformed for presentation and inclusion in models due to large positive skew.

Potential confounders/effect modifiers included were body mass index (BMI) and/or height (cm) and weight (kg) variables, as well as age, years of education, and sex.

**Study Size**

We initially invited 2,000 people to participate but increased this to 3,000 to achieve the required sample size. Participants were stratified into two age groups: 18–39 years and ≥40 years. We estimated that, after allowing for unequal age and sex distributions, refusals, and inability to provide spirometry measurements of acceptable quality, a sample of just 300 participants in any one sex/age stratum (1,200 total) would provide an estimate of chronic airflow limitation prevalence in this stratum with a precision (95% confidence interval [CI]) of ±3.3% to ±5.0% assuming a prevalence of 10–25%.

**Statistical Analyses**

Univariate analysis was completed using descriptive statistics to explore the characteristics of the study population. Descriptive analysis is presented for clarity using categorical versions of BMI (underweight, normal, overweight, or obese) and categorical versions of age; however, age, weight, and height were entered into models as continuous variables. Participants who completed the study in full or in part were assessed for selection bias using the $\chi^2$ and Student’s $t$ tests. Multivariable logistic regression was used to estimate the strength of the association between measured exposure variables and dichotomous clinical outcomes, adjusting for potential confounders. All models were adjusted for age, sex, weight, and height. Linear multivariable regression was used to estimate the association between exposures and continuous lung function values (FEV$_1$, FVC, and FEV$_1$/FVC). Secondary exploratory trial efficacy analyses were by intention to treat. Statistical significance was nominally set at $\alpha = 0.05$. Stata version 14.2 and R version 3.4 statistical software was used for data analysis (Stata statistical software: R.14; StataCorp, LLC).

**Role of the Funding Source**

The funders had no role in the study design, data collection, analysis, interpretation, or writing of the report. The corresponding author had full access to all the study data and had final responsibility for the decision to submit for publication.

**Results**

**Table 1. Demographic and Clinical Characteristics ($N=1,481$)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Level</th>
<th>n (%) or Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group, yr</td>
<td>&lt;39</td>
<td>686 (46.32)</td>
</tr>
<tr>
<td></td>
<td>40–49</td>
<td>259 (17.49)</td>
</tr>
<tr>
<td></td>
<td>50–59</td>
<td>216 (14.58)</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>160 (10.80)</td>
</tr>
<tr>
<td></td>
<td>&gt;70</td>
<td>160 (10.80)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>637 (43.01)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>844 (56.99)</td>
</tr>
<tr>
<td>Education</td>
<td>None</td>
<td>485 (32.79)</td>
</tr>
<tr>
<td></td>
<td>Primary</td>
<td>758 (51.25)</td>
</tr>
<tr>
<td></td>
<td>Middle</td>
<td>205 (13.86)</td>
</tr>
<tr>
<td></td>
<td>High school or college</td>
<td>31 (2.10)</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>2 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Years of education, mean (SD)</td>
<td>4.20 (4.09)</td>
</tr>
<tr>
<td></td>
<td>Years of education if any, mean (SD)</td>
<td>6.31 (3.44)</td>
</tr>
<tr>
<td>Smoking</td>
<td>Never smoker</td>
<td>1,152 (77.8)</td>
</tr>
<tr>
<td></td>
<td>Current or ever smoker</td>
<td>328 (22.2)</td>
</tr>
<tr>
<td>Pack-years of smoking</td>
<td>0</td>
<td>1,152 (77.8)</td>
</tr>
<tr>
<td></td>
<td>Up to 10 pack-years</td>
<td>263 (17.8)</td>
</tr>
<tr>
<td></td>
<td>&gt;10 pack-years</td>
<td>63 (4.3)</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>3 (0.0)</td>
</tr>
<tr>
<td>BMI group, kg/m$^2$</td>
<td>Underweight (BMI, &lt;18.5)</td>
<td>188 (14.4)</td>
</tr>
<tr>
<td></td>
<td>Normal (BMI, 18.5–25)</td>
<td>945 (72.5)</td>
</tr>
<tr>
<td></td>
<td>Overweight (BMI, 25–30)</td>
<td>130 (10.0)</td>
</tr>
<tr>
<td></td>
<td>Obese (BMI, &gt;30)</td>
<td>40 (3.1)</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>178 (12.0)</td>
</tr>
<tr>
<td>Previous TB</td>
<td>No</td>
<td>1,434 (92.3)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>47 (3.2)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Cough (Do you usually cough when you don’t have a cold?)</td>
<td>165 (11.1)</td>
</tr>
<tr>
<td></td>
<td>Sputum (Do you usually bring up phlegm from your chest?)</td>
<td>38 (2.6)</td>
</tr>
<tr>
<td></td>
<td>Wheeze (Have you had wheezing/whistling in your chest at any point in past 12 months in the absence of a cold?)</td>
<td>23 (1.6)</td>
</tr>
<tr>
<td></td>
<td>MRC dyspnea II (Do you have shortness of breath when hurrying on the level or walking up a slight hill?)</td>
<td>23 (1.6)</td>
</tr>
<tr>
<td></td>
<td>Any respiratory symptoms (Any of cough, sputum, wheeze without cold, exertional breathlessness as above?)</td>
<td>201 (13.6)</td>
</tr>
<tr>
<td></td>
<td>Functional limitation (Have breathing problems interfered with your usual daily activities?)</td>
<td>43 (2.9)</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** BMI = body mass index; MRC = Medical Research Council; TB = tuberculosis. Data are n (%) unless otherwise indicated.
sampled to invite them to participate, of whom 1,481 (49.4%) consented and completed BOLD study questionnaires. Of these, 950 (64.6%) went on to do spirometry; the remaining 520 (35.3%) were unable to do spirometry because they could not physically cooperate with the procedure (n = 258; 48.9%), had a fieldworker-determined contraindication (n = 193; 37%), or refused (n = 69; 13.3%). Of the 1,481 participants, 1,144 (77.2%) underwent personal air pollution exposure monitoring. There were 424 (28.6%) participants from CAPS intervention or control households (Figure 1).

The mean age (SD) of participants was 43.8 (17.8) years and 57% were female (Table 1). Just more than half of the participants had been educated only to primary school level, with a third having had no formal school education. The use of biomass fuels for cooking was almost universal (99.8%).

One or more chronic respiratory symptom was reported by 201 (13.6%; 95% CI, 13.1–14.1) participants (Table 1 and Figure 2). Respiratory symptoms were more commonly reported with increasing age. Regular cough was reported by 11.1% (95% CI, 10.6–11.6) while 2.6% (95% CI, 2.2–3.1) reported usually coughing up phlegm. Breathlessness and wheeze were less commonly reported: 1.6% (95% CI, 1.0–2.3) and 1.6% (95% CI, 1.0–2.3), respectively. Respiratory symptoms that limited functional ability were reported by 2.9% (95% CI, 2.2–3.9). A previous diagnosis of TB was reported by 3.2% (95% CI, 2.4–4.2), which was more common with increasing age. Current or former smoking was reported by 22.1% (95% CI, 20.1–24.3), although only 4.3% had a >10 pack-year history. Many participants (14.4%) had a low BMI.

Of the 950 participants who did spirometry, 886 (93.2%) achieved BOLD study quality standards and were included in the analyses. Factors associated with declining or not completing spirometry to European Respiratory Society/American Thoracic Society standards were older mean age (48 vs. 39 yr; P < 0.001), being female (65% vs. 51%; P < 0.001), lower mean years of education (2 vs. 5 yr; P < 0.001), and lower mean BMI (20.7 vs. 21.3; P < 0.001). As shown in Table E1 in the online supplement, participants who completed spirometry were less likely to have cough, wheeze, and dyspnea compared with those who did not complete spirometry and were slightly more likely to have phlegm and functional limitation, although none of these differences was statistically significant. Spirometric obstruction and restriction were present in 8.7% (95% CI, 7.0–10.7) and 34.8% (95% CI, 31.7–38.0) of the 886 participants who met the required quality standards, respectively.

Of the 1,144 participants (mean age [SD], 43.9 [17.9] yr; 57% female) who underwent personal exposure monitoring, 1,117 (97.6%) had valid exposure monitoring records. The 48-hour median personal PM$_{2.5}$ and CO exposures were 71.0 μg/m$^3$ (interquartile range [IQR], 44.6–119.2) and 1.23 ppm (IQR, 0.79–1.93), respectively. There was weak correlation between these two air pollution exposure measures (Figure 3).

In logistic multivariable analysis, smoking (odds ratio [OR], 1.56; 95% CI, 1.01–2.41) and previous TB (OR, 2.81; 95% CI, 1.19–6.08) were associated with cough (Table 2 and Table E1). In continuous multivariable analysis, both FEV$_1$ and FVC had a negative association with increasing age and were higher for men compared with women (Table 3). Smoking (coefficient estimate, –0.09; 95% CI, −0.16 to −0.01) and previous TB (coefficient estimate, −0.46; 95% CI, −0.64 to −0.28) were associated with FEV$_1$, and previous TB was associated with FVC (coefficient estimate, −0.35; 95% CI, −0.56 to −0.15). There was no association between personal exposure to PM$_{2.5}$ and any of the demographic and clinical characteristics or spirometric

![Figure 2](image-url). Age-stratified prevalence of respiratory symptoms.
The only statistically significant association was between exposure to CO and reporting "any chronic respiratory symptoms" (OR, 1.46; 95% CI, 1.04–2.05). There were no statistically significant associations between personal exposure to CO and any other demographic and clinical characteristics or to any spirometric indices. There were 424 (227 intervention; 197 control) participants in the CAPS intention-to-treat population; however, not all of them had complete spirometry (133 without) or exposure measures (87 without). There were no differences in respiratory symptoms, spirometric indices, or exposure to CO or PM$_{2.5}$ between the intervention and control groups (Table 6).

**Discussion**

The main findings of this cross-sectional study of the burden and determinants of noncommunicable respiratory disease in adults living in Chikhwawa, rural Malawi, were that: 13.6% of participants had chronic respiratory symptoms (mainly cough); >40% had abnormal spirometry (mainly spirometric restriction); day-to-day air pollution exposures were approximately three times the WHO upper safety limit; and there was no association between CAPS trial arm and any of the secondary trial outcomes in the subset of adults included both in this study and the trial. The finding of a low prevalence of spirometric obstruction in this setting—where highly polluting fuels are almost universally used for household energy needs and where exposure to household air pollution is high—is surprising given that household air pollution–associated COPD has been suggested to be a major global health problem and as such would be expected to be highly prevalent in our study setting (16–19). This finding is consistent with an emerging body of evidence challenging the dogma that exposure to household air pollution is a major cause of COPD, including a recent pooled analysis of BOLD study data from low-, middle-, and high-income countries (20). This analysis found no association between spirometric obstruction and self-reported use of solid fuels for cooking or heating. This is, however, an area of controversy, with investigators disagreeing about the interpretation of the available data (21, 22).

Many of the studies conducted to date looking at the association between COPD and exposure to household air pollution have had important methodological

### Table 2. Odds Ratios (95% Confidence Interval) for Chronic Respiratory Symptom Outcomes Estimated by Multivariable Logistic Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cough</th>
<th>Phlegm*</th>
<th>Wheeze*</th>
<th>Dyspnea*</th>
<th>Functional Limitation</th>
<th>Any Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>1.01 (1.00–1.02)</td>
<td>1.00 (0.97–1.02)</td>
<td>1.02 (0.99–1.05)</td>
<td>1.01 (0.98–1.04)</td>
<td>1.00 (0.95–1.02)</td>
<td>1.00 (0.97–1.02)</td>
</tr>
<tr>
<td>Female</td>
<td>0.78 (0.49–1.25)</td>
<td>1.02 (0.42–2.51)</td>
<td>0.97 (0.30–3.28)</td>
<td>3.08 (0.88–11.65)</td>
<td>1.17 (0.28–2.37)</td>
<td>1.08 (0.70–1.67)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>1.56 (1.01–2.41)</td>
<td>1.37 (0.58–3.15)</td>
<td>0.77 (0.20–2.47)</td>
<td>1.85 (0.51–6.07)</td>
<td>0.65 (0.18–1.93)</td>
<td>1.59 (1.05–2.39)</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>2.81 (1.19–6.08)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2.64 (0.40–9.95)</td>
<td>2.50 (1.04–15.58)</td>
</tr>
<tr>
<td>Years of education</td>
<td>0.97 (0.92–1.02)</td>
<td>0.90 (0.81–1.00)</td>
<td>0.99 (0.86–1.13)</td>
<td>0.96 (0.83–1.10)</td>
<td>1.06 (0.96–1.16)</td>
<td>0.98 (0.93–1.03)</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: Ref = reference; TB = tuberculosis.*

*Only one person had both TB and wheeze, one person had both TB and phlegm, and one person had both TB and dyspnea; TB was excluded from these models.*
Table 3. Coefficient Estimates (95% Confidence Interval) for Continuous Spirometry Outcomes FEV₁, FVC, and FEV₁/FVC Ratio (n = 886)

<table>
<thead>
<tr>
<th>Variable</th>
<th>FEV₁</th>
<th>FVC</th>
<th>FEV₁/FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>−0.02 (−0.02 to −0.02)</td>
<td>−0.01 (−0.01 to −0.01)</td>
<td>−0.28 (−0.31 to −0.24)</td>
</tr>
<tr>
<td>Male</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Female</td>
<td>−0.53 (−0.60 to −0.45)</td>
<td>−0.70 (−0.78 to −0.62)</td>
<td>1.37 (0.18 to 2.56)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>−0.09 (−0.16 to −0.01)</td>
<td>−0.05 (−0.14 to 0.04)</td>
<td>−1.76 (−2.99 to −0.53)</td>
</tr>
<tr>
<td>Previous TB: no</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Previous TB: yes</td>
<td>−0.46 (−0.64 to −0.28)</td>
<td>−0.36 (−0.56 to −0.15)</td>
<td>−7.83 (−10.74 to −4.91)</td>
</tr>
<tr>
<td>Years of education</td>
<td>0 (0 to 0.01)</td>
<td>0 (−0.01 to 0.01)</td>
<td>0.18 (0.05 to 0.3)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: Ref = reference; TB = tuberculosis.
All models were also adjusted for weight (kg) and height (cm).

Table 4. Odds Ratios (95% Confidence Interval) for Symptom Outcomes Estimated by Multivariable Logistic Regression in Participants with Exposure Measurements (n = 985)

<table>
<thead>
<tr>
<th>Ever smoked (ref: never smoked)</th>
<th>Cough</th>
<th>Phlegm*</th>
<th>Wheeze*</th>
<th>Dyspnea*</th>
<th>Functional Limitation</th>
<th>Any Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.72 (1.02−2.91)</td>
<td>0.99 (0.37−2.53)</td>
<td>0.35 (0.02−2.32)</td>
<td>2.62 (0.56−11.24)</td>
<td>0.78 (0.20−2.47)</td>
<td>1.67 (1.02−2.71)</td>
</tr>
<tr>
<td>Previous TB: no</td>
<td>2.87 (1.07−6.87)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3.00 (0.51−17.4)</td>
<td>2.47 (0.91−6.07)</td>
</tr>
<tr>
<td>Previous TB: yes</td>
<td>1.29 (0.93−1.77)</td>
<td>1.50 (0.83−2.54)</td>
<td>2.12 (0.96−4.16)</td>
<td>1.27 (0.48−2.88)</td>
<td>1.45 (0.81−2.43)</td>
<td>1.46 (1.04−2.05)</td>
</tr>
<tr>
<td>CO (log₁₀ ppm)</td>
<td>1.02 (0.95−1.13)</td>
<td>0.96 (0.88−1.11)</td>
<td>1.00 (0.87−1.38)</td>
<td>1.11 (0.89−1.67)</td>
<td>0.99 (0.90−1.16)</td>
<td>1.02 (0.95−1.11)</td>
</tr>
<tr>
<td>PM2.5 (log₁₀ μg/m³)</td>
<td>1.02 (0.95−1.13)</td>
<td>0.96 (0.88−1.11)</td>
<td>1.00 (0.87−1.38)</td>
<td>1.11 (0.89−1.67)</td>
<td>0.99 (0.90−1.16)</td>
<td>1.02 (0.95−1.11)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: CO = carbon monoxide; PM₂.₅ = particulate matter <2.5 μm in aerodynamic diameter; ref = reference; TB = tuberculosis. All models were adjusted for weight (kg), height (cm), age (yr), sex (male, female), and years of formal education.

*Only one person had both TB and wheeze, one person had both TB and phlegm, and one person had both TB and dyspnea; TB was excluded from these models.


Table 5. Coefficient Estimates (95% Confidence Interval) for Continuous Spirometry Outcomes FEV₁, FVC, and FEV₁/FVC Ratio in Participants with Personal Air Pollution Exposure Measurements (n = 886)

<table>
<thead>
<tr>
<th>Variable</th>
<th>FEV₁</th>
<th>FVC</th>
<th>FEV₁/FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>-0.02 (-0.02 to -0.01)</td>
<td>-0.01 (-0.02 to -0.01)</td>
<td>-0.28 (-0.35 to -0.20)</td>
</tr>
<tr>
<td>Male</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Female</td>
<td>-0.58 (-0.61 to -0.44)</td>
<td>-0.70 (-0.79 to -0.60)</td>
<td>1.25 (-0.09 to 2.56)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>-0.1 (-0.19 to -0.02)</td>
<td>-0.07 (-0.16 to 0.03)</td>
<td>-1.83 (-3.20 to -0.45)</td>
</tr>
<tr>
<td>Previous TB: no</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Previous TB: yes</td>
<td>-0.32 (-0.52 to -0.11)</td>
<td>-0.26 (-0.49 to -0.02)</td>
<td>-6.16 (-9.48 to -2.85)</td>
</tr>
<tr>
<td>Years of education</td>
<td>0 (0 to 0.01)</td>
<td>0 (-0.01 to 0.01)</td>
<td>0.15 (0.01 to 0.29)</td>
</tr>
<tr>
<td>CO (log₁₀ ppm)</td>
<td>0.01 (-0.04 to 0.06)</td>
<td>0.01 (-0.04 to 0.07)</td>
<td>0.13 (-0.08 to 0.04)</td>
</tr>
<tr>
<td>PM₂.₅ (log₁₀ μg/m³)</td>
<td>0 (-0.02 to 0.01)</td>
<td>0 (-0.01 to 0.01)</td>
<td>-0.11 (-0.29 to 0.08)</td>
</tr>
</tbody>
</table>

For definition of abbreviations, see Table 4. All models were also adjusted for weight (kg) and height (cm).

of effect of the CAPS intervention on these outcomes include insufficient levels of intervention adoption, insufficient reductions in emissions and exposures, and other sources of air pollution exposure overwhelming any potential effect of the intervention (5).

A notable observation of this study was that 35% of participants had spirometric restriction when benchmarked against NHANES III white reference range values. We consider the approach we have taken of benchmarking against the NHANES III white reference ranges as the best we can do at this time while accepting that this and all other currently available alternatives are not ideal. That includes locally derived reference ranges that might be helpful in defining what is ‘usual’ lung function in asymptomatic non-smoking Malawian adults but that may be far from ‘optimal potential normal lung function.’ Because there is evidence that the prognostic significance of spirometric restriction holds irrespective of racial/ethnic group when benchmarked in this way (23, 24), the finding of such a high burden of spirometric restriction in the rural Malawian population, and elsewhere in sub-Saharan Africa (25, 26), is of considerable concern; observational cohort studies are needed to understand the clinical characteristics and prognostic significance of these findings. The underlying drivers of spirometric restriction in sub-Saharan African populations are not yet understood, but we hypothesize that these are primarily environmental insults experienced in early life (e.g., malnutrition, infections and air pollution exposures before conception, in utero, and during childhood) such that adulthood is reached without maximal potential lung function having been achieved. Cross-sectional studies of the burden and determinants of noncommunicable lung disease in children in sub-Saharan Africa are needed to explore whether the same patterns of abnormality are seen in early life and, if so, studies even earlier in the life course to identify potential windows of opportunity to intervene to maximize lung health.

Strengths of this study include that it was conducted in a highly challenging research setting in one of the world’s poorest rural communities as part of the CAPS protocol; it is the first of the global BOLD studies to be conducted in a rural sub-Saharan African setting and it is also the first BOLD study to incorporate personal air pollution exposure measurements and to do so at scale. Limitations include questionnaire assessments for most variables with potential for recall bias; the potential bias (e.g., underestimation of the burden of spirometric abnormalities) caused by participants who did not do spirometry, although the quality of those that did spirometry was generally high; and air pollution exposure assessments that provided only a 48-hour snapshot of exposure and were based on a light-scattering method alone for PM₂.₅.

In conclusion, we found that exposures to air pollution among Malawian adults living in communities participating in CAPS were at levels well beyond those considered safe by the WHO. In keeping with the primary outcome of the CAPS trial, we found no effect of the intervention on any of

Table 6. CAPS Intention-to-Treat Secondary Trial Analyses (n = 424)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention (n = 227)</th>
<th>Control (n = 197)</th>
<th>Intervention vs. Control Coefficient Estimate (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms, n (%)</td>
<td>22 (8.7)</td>
<td>26 (13.2)</td>
<td>0.90 (0.45 to 1.82)*</td>
<td>0.87</td>
</tr>
<tr>
<td>FEV₁, median (IQR)</td>
<td>2.81 (2.39 to 3.26)</td>
<td>2.77 (2.40 to 3.10)</td>
<td>0.08 (-0.06 to 0.22)</td>
<td>0.26</td>
</tr>
<tr>
<td>FVC, median (IQR)</td>
<td>3.37 (2.88 to 3.91)</td>
<td>3.31 (2.83 to 3.86)</td>
<td>0.04 (-0.13 to 0.21)</td>
<td>0.62</td>
</tr>
<tr>
<td>Mean CO, median (IQR)</td>
<td>1.13 (0.79 to 1.90)</td>
<td>1.28 (0.82 to 1.79)</td>
<td>0.67 (-0.60 to 1.96)</td>
<td>0.30</td>
</tr>
<tr>
<td>Mean PM₂.₅, median (IQR)</td>
<td>67.90 (44.72 to 112.95)</td>
<td>64.47 (40.73 to 101.80)</td>
<td>-0.913 (-2.073 to 0.209.7)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

*Odds ratio (95% CI).

Definition of abbreviations: CAPS = Cooking and Pneumonia Study; CI = confidence interval; CO = carbon monoxide; IQR = interquartile range; PM₂.₅ = particulate matter <2.5 μm in diameter.

Mean exposure per individual is calculated, and the median (IQR) of those values is reported.
Obstruction (and household air pollution–associated COPD) than has been thought to exist. There is a need to explore other plausible explanations for the poor lung function observed in these and other low- and middle-income country populations, including further exploration of the role of TB, recurrent pneumonia, and nutrition. Clinically effective and cost-effective approaches for the prevention and control of noncommunicable respiratory diseases are very much needed in sub-Saharan Africa.

Acknowledgment: The authors thank the trial participants, village leaders, and CAPS representatives, the study team in Chikhwawa, Malawi–Laverty–Wellcome Trust Clinical Research Programme and Liverpool School of Tropical Medicine, the CAPS trial steering committee and data monitoring committee, the Malawi Ministry of Health, the Aprovecho Research Centre, the African Clean Energy company, and the BOLD Centre for their valued contributions to making this work a success. We thank Stephen Gordon for comments on the paper.

Author disclosures are available with the text of this article at www.atsjournals.org.

References
Section 2: Supplement to Paper

Online Data Supplement

Table E1: OR (95% CI) for chronic respiratory symptom outcomes estimated by multivariable logistic regression as shown in Table 2 but with the addition of a variable for completing or not completing spirometry

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cough</th>
<th>Phlegm**</th>
<th>Wheeze**</th>
<th>Dyspnoea**</th>
<th>Functional limitation</th>
<th>Any symptoms</th>
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<tbody>
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<td>1·02</td>
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<td></td>
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</tr>
<tr>
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<td>0·73</td>
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</tr>
</tbody>
</table>
All models also adjusted for weight (kg), height (cm); ** Only one person had both TB and wheeze or TB and phlegm or TB and dyspnoea, TB was excluded from these models.

Ethics and patient information sheet were as part of a larger project and not completed by myself and therefore not included.
Appendix for Chapter Five

Section 1: PDF of Paper
Non-communicable respiratory disease in Malawi: a systematic review and meta-analysis

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3. Population Health Science Institute, Newcastle University, Newcastle, UK
4. Ministry of Health, Government of Malawi, Malawi
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*Joint first authors.
†Joint last authors.

Abstract

Background
Non-communicable respiratory diseases are important contributors to morbidity and mortality in sub-Saharan African countries such as Malawi.

Aim
To conduct a systematic review of the available literature relating to chronic respiratory disease in Malawi.

Methods
We conducted a systematic protocol-driven literature search of key scientific databases including Scopus and Medline. Papers were independently assessed for eligibility by two authors and included if they reported objective measures (including self-reported standard symptoms) of chronic respiratory disease and were conducted in Malawi. A meta-analysis of available estimates was then conducted. We re-analysed data from three of these studies in a secondary data analysis to allow for between-study comparisons.

Results
Our search identified 393 papers of which 17 (5 involving children and 12 involving adults) met the inclusion criteria. Wheeze was the symptom most frequently reported in children in the community (12.1%), hospital (11.2%) and HIV clinic (8.1%) settings. Cough was the symptom most frequently reported by adults in the community (3–18%). Spirometric abnormalities varied substantially between studies. For example, in adults, airflow obstruction varied between 2.3% and 20% and low forced vital capacity (FVC) varied between 2.7% and 52.8%.

Conclusion
We identified a high burden of chronic respiratory symptoms and abnormal spirometry (particularly low FVC) within paediatric and adult populations in Malawi. The estimates for country-wide burden related to this disease were limited by the heterogeneity of the methods used to assess symptoms and spirometry. There is an urgent need to develop a better understanding of the determinants and natural history of non-communicable respiratory disease across the life-course in Malawi.

Key Words: COPD, asthma, chronic lung disease, cough, non-communicable disease, Malawi

Introduction
Non-communicable diseases (NCDs) kill 41 million people globally, accounting for 71% of deaths worldwide1. More than three quarters (32 million) of these deaths occur in low- and middle-income countries (LMICs), including LMICs in sub-Saharan Africa, such as Malawi. Health policy has historically focussed on communicable rather than non-communicable disease in sub-Saharan African countries3, although the need to prioritise the prevention and control of NCDs is increasingly recognised, with the Malawi National Health Research Agenda highlighting the fact that chronic lung disorders are a priority research area for the country3,4. Non-communicable respiratory diseases are major contributors to NCD mortality with 3.6 million attributable deaths globally in 20155. Of these diseases, asthma and chronic obstructive pulmonary disease (COPD) are the most common6,10. The International Study of Asthma and Allergies in Childhood (ISAAC) estimated the prevalence of asthma using standardised questionnaires in 105 countries11. In the seven countries from sub-Saharan Africa, the prevalence of asthma varied between 9.1% in Ethiopia and 20.3% in South Africa11. The prevalence of COPD has been estimated from cross-sectional spirometry-based studies, including the International Burden of Obstructive Lung Disease (BOLD) initiative12. The highest prevalence was seen in Cape Town, South Africa where moderate to severe obstruction was present in 19.1% of the adult population whilst prevalence in Ile-Ife (Nigeria), urban Blantyre (Malawi) and rural Chikwawa (Malawi) were 7.7%, 3.6% and 8.7%, respectively13,14. Recently, two further studies have reported lower levels of obstruction in Uganda: 6.1% and 2% in rural populations, and 1.5% in an urban population15,16.

We conducted a systematic review and pooled analysis of the burden of NCDs and the risk factors associated with NCDs in Malawi. This review adopted a broad approach and focused on any population, any intervention, any comparison technique, any outcome, and any study design.

Methods

Systematic review
This systematic review is registered with the Centre for Reviews and Dissemination (Registration number: CRD42018117325). The full protocol is available at http://

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Eligibility criteria
Publications were included if they described the burden of non-communicable respiratory diseases (including COPD, asthma, low forced vital capacity (FVC)/restrictive disease and bronchiectasis) in Malawian individuals of any population (any sex or age), involving any intervention and outcomes linked to non-communicable respiratory disease. We included any form of study design, including studies that defined non-communicable respiratory diseases using symptoms, self-reported diagnosis, doctor diagnosis, and spirometry.

Search strategy
The databases and grey literature listed in Box 1 were searched using the specific search terms and Boolean phrases listed in Box 2 and the search strategy set out in Box 3. Identified papers were then imported into EndNote X7. The reference lists of all selected papers were also reviewed to identify any potentially eligible titles. For studies where relevant details were not available, authors were invited to supply information if their contact details were available.

Box 1: Databases and Grey Literature
Databases:
- Scopus (including EMBASE)
- MEDLINE (OVID)
- Web of Science
- Cochrane Central Register of Controlled Trials (CENTRAL)
- CINAHL (OVID)
- SciELO
Grey literature:
- World Health Organization Clinical Trials Registry
- www.clinicaltrials.gov
- European Association for Grey Literature Exploitation (EAGLE)

Box 2: Search terms and Boolean phrases used
Outcomes (OR): “chronic respiratory” OR “non-communicable lung” OR “chronic obstructive pulmonary disease” OR “COPD” OR “asthma” OR “obstructive lung” OR “restrictive lung” OR “obstructive respiratory” OR “restrictive respiratory” OR “obstructive airway*” OR “restrictive airway*” OR “spiromet*” OR “wheeze” OR “chronic cough” OR “shortness of breath” OR “breathlessness” OR “chronic sputum” AND Location: “Malawi”

Data extraction
Data were extracted by HJ and RN from the selected papers using a data extraction form (which had been pre-tested). These forms were used to create summary tables and narrative syntheses. Data extraction was independently checked by ML. We also collated information regarding exposure to household air pollution, smoking and previous TB, where available.

Methodological quality assessment
The methodological quality of the selected studies was assessed by HJ using the Newcastle-Ottawa Scale for cohort and case-control studies (scored out of 5) and a modified version of the Newcastle-Ottawa Scale for cross-sectional studies (scored out of 5) (Table 1).

Statistical analysis
Published estimates of the prevalence of symptoms, obstruction or low FVC, and mean (standard deviation [SD]) and median (interquartile range [IQR]) carbon monoxide (CO), and fine particulate matter (PM$_{2.5}$) were extracted for meta-analysis. We then created Forest plots using the estimated proportion and 95% confidence intervals. Meta-analysis estimates of overall prevalence were stratified by age group (adult, paediatric) and estimated using the DerSimonian-Laird random effects model (R package metaviz)$. Estimates derived from meta-analysis were only calculated for outcomes in which the studies were deemed to be adequately homogenous. Estimates of measures of heterogeneity ($I^2$, $tau^2$) and an overall Q-test were generated using linear mixed effects models (R package metaphor) and reported. Publication bias was evaluated by visual inspection of funnel plots.

Data from three of the studies included in the meta-analysis that had been performed using the same core BOLD protocol were re-analysed in order to provide comparable estimates: the Adult Lung Health Study (ALHS), the
Blantyre Health Study (BHS), and the Acute Infection of the Respiratory tract Study (AIR Study)\textsuperscript{15,16,20}. This allowed for the pooled analysis of data which had not previously been performed (referred to subsequently as the “pooled analysis” to distinguish this from the “meta-analysis”). Details of the sampling and measurement procedures for these three studies have been described previously; consequently, we restricted our description of these methods to the secondary analysis presented here\textsuperscript{12,13,15,16,20,21}. The prevalence (with SD) of symptoms, exposures, obstruction, and low FVC, were estimated using a combination of the three data sources, and is referred to as “pooled data” hereafter. We also calculated median (IQR) estimates for CO and PM\textsubscript{2.5} exposure.

**Figure 2.** Funnel plots for lung function estimates in paediatric (blue) and adult (red) populations. Panel A (left): restriction, Panel B (right) obstruction.
Non-communicable respiratory disease in Malawi

Ethics
Liverpool School of Tropical Medicine provided ethical approval for all three studies which we included for secondary data analysis (Reference numbers: 12.08, 12.40 and 14.016). The ALHS and AIR were approved by the College of Medicine Research and Ethics Committee, Malawi (References: p.11/12/1308 and P.02/14/1518, respectively), and the BHS was approved by the National Research and Ethics Committee of Malawi (Reference: 12.08). All participants provided informed consent.

Results
Study selection
Database and grey literature searches on 9 October 2018 and updated on 3 June 2019 identified 393 titles for review; 17 papers met the inclusion criteria (Figure 1). Funnel plots were limited by the small number of studies but were relatively symmetrical ($P=0.017$ for obstruction and $P=0.032$ for restriction, as determined by the Eager test) (Figure 2).

Quality assessment
Analyses showed that the included studies were of variable quality. Studies that had been specifically designed to assess the burden of non-communicable respiratory disease were found to be of the highest quality (Table 1).

Study characteristics
The studies incorporated cohort ($n=1$), case-control ($n=1$), and cross-sectional ($n=15$) study designs (or included a cross-sectional description of non-communicable respiratory disease burden nested within a Randomised Controlled Trial or economic evaluation) (Table 2). Five studies reported paediatric populations, while 12 reported adult populations; one of the studies included a population from 10 to 65 years of age (Table 2). Nine studies were from urban settings only (four healthcare or clinic-based, three community-based, and the case-control and cohort studies were performed in both community and health care settings); five were from rural settings only (all community-based), and three studies incorporated both rural and urban settings (all community-based).

Symptoms
Thirteen studies assessed self-reported respiratory symptoms or diagnoses using questionnaires; of these, five used BOLD questionnaires (Table 3). In the paediatric population, the most commonly reported symptom in the community was wheeze, with a prevalence of 12.1%, followed by cough (prevalence 8%) [24]. In the two studies related to the prevalence of symptoms in hospital clinics, cough was more common (41.7% and 37.5%) than wheeze (11.2% and 8.1%) [23, 24]. Our meta-analysis estimated that the prevalence of cough symptoms in children was 29.1 ± 10.6% ($P=0.0059$, $I^2=98\%$, Q-test $P<0.0001$) (Figure 3).

Within the adult populations in the community, cough was the most commonly reported symptom (range: 3–18.6%), followed by shortness of breath (range: 1.6–13%). Productive cough and phlegm production were less commonly reported (range: 0.2–9% and 1.4–5.9% respectively). Our meta-analysis and pooled analysis estimates for prevalence of cough symptoms in adults were 13.3±10.6%, $P<0.0001$.

| Table 1. The risk of bias, as determined by the Newcastle-Ottawa Scale |
|--------------------------|--------------------------|--------------------------|--------------------------|
| Case-control and cohort studies | Selection (out of 4) | Comparability (out of 2) | NCLD assessment (out of 3) | Overall score (out of 9) |
| Jary et al., 2017 | 3 | 2 | 2 | 7 |
| Lelijveld et al., 2017 | 3 | 2 | 2 | 7 |
| Descriptive cross-sectional studies | Selection (out of 3) | NCLD assessment (out of 2) | Overall score (out of 5) |
| Zverev et al., 2001 | 1 | 2 | 3 |
| Fullerton et al., 2011 | 2 | 2 | 4 |
| To et al., 2012 | 2 | 1 | 3 |
| Cook et al., 2013 | 1 | 2 | 3 |
| Jary et al., 2014 | 1 | 0 | 1 |
| Manjomo et al., 2016 | 2 | 0 | 2 |
| Meghji et al., 2016 | 2 | 2 | 4 |
| Mwalukomo et al., 2016 | 1 | 2 | 3 |
| Wang et al., 2016 | 0 | 0 | 0 |
| Banda et al., 2017 | 2 | 1 | 3 |
| Das et al., 2017 | 1 | 1 | 2 |
| Towned et al., 2017 | 1 | 2 | 3 |
| Cohen et al., 2019 | 1 | 1 | 2 |
| Nightingale et al., 2019 | 2 | 2 | 4 |
| Rylance et al., 2019 | 2 | 2 | 4 |

NCLD: non-communicable lung disease.
Lung function

Eight of the nine studies (four paediatric and four adult) that performed spirometry reported data that were collected in accordance with standards reported by the American Thoracic Society (ATS)/European Respiratory Society (ERS). However, five different ranges were used and a mix of raw values, proportional (%) predicted values and Z-scores were used in analysis.\cite{20,23-27,33-35} (Table 4).

One study, a community-based cross-sectional study, focused on peak expiratory flow rate (PEFR) in stunted children, reported that PEFR was reduced in those with poor growth.\cite{20} In paediatric community populations, 6.6–9.0% of the population had obstruction while 6.6–7.5% had low FVC. In those with sickle cell disease and HIV infection, obstructive spirometry was identified in 0 and 18% of cases while low FVC was detected in 25% and 17% of cases, when using local reference ranges (58% and 20% if using international reference ranges), respectively.\cite{23,24} The cohort study that assessed lung function in malnourished children reported a reduced FEV\textsubscript{1} (forced expiratory volume in the first second) and FVC in all study groups, but with no significant difference between paediatric survivors of severe acute malnutrition and healthy controls.\cite{25} The diagnosis of asthma in children, based on spirometry and questionnaires, was reported in 3.9% of the community or 12.1% if wheeze was used as the definition; asthma was also reported in 4.2% of children with sickle cell anaemia.\cite{23,26} None of the studies used the same definition for asthma in the same way.

The range of obstruction reported in adults where spirometry had been completed was 2.3–20% with low FVC varying from 2.7% to 52.8%. The use of different ranges within the same population resulted in a prevalence of obstruction of 2.3–4.2%, and low FVC of 9–38.6%, using local and NHANES (National Health and Nutrition Examination Survey) Caucasian ranges, respectively.\cite{15,16} The prevalence of asthma in adults ranged from 0% to 12.2% with a mixture of diagnostic types: doctor diagnosis (7.6–12.2%), self-reported (4.7–8%) and diagnoses involving spirometry (0–4.2%).\cite{16,18,25,26,28,30-32} In our meta-analysis, the prevalence of obstruction in adults was 8.3 ± 2.4%, $P$ = 0.0007, $I^2$ = 89%, Q-test $P$ < 0.0001, and low FVC 31 ± 7.2%, $P$ < 0.0001, $I^2$ = 97%, Q-test $P$ < 0.0001 (Figure 2). Pooled analysis estimated overall FEV\textsubscript{1} of 2.64 L (0.69), FVC of 3.28 L (0.77) and FEV\textsubscript{1}/FVC of 80.5% (8.48). The pooled prevalence of obstruction was 8.4% and low FVC was 37.5% (NHANES) or 16.3% (using the local range).

Risk factors

The most commonly reported risk factors for non-communicable respiratory disease were the use of biomass fuel and smoking. Exposure to biomass fuel was assessed in a variety of different ways in different studies. In paediatric studies, 14–83% of the study populations were exposed to biomass fuels (Table 3). In adult studies, self-reported exposure to biomass fuel was reported in

Figure 3. Forest plots and meta-analysis estimates for symptoms (A–D), exposure (E, F) and respiratory outcomes (G, H). SOB: shortness of breath.
The self-reported prevalence of smoking (“ever smoked”) ranged from 1% to 28.2% in the adult population. Previous TB and low BMI were considered as possible risk factors in the BOLD studies. Meta-analysis and pooled analysis of associations between risk factors and lung function was not possible due to the incomplete nature of reporting across different studies.

### Table 2. Summary of the main findings from literature searches (date order)

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Year</th>
<th>Rural/Urban</th>
<th>Mean Age (years)</th>
<th>Setting and study design</th>
<th>Sample size</th>
<th>Assessment methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zverev</td>
<td>2001</td>
<td>Urban</td>
<td></td>
<td>Children in primary school, children from each class were randomly selected</td>
<td>539</td>
<td>Peak expiratory flow only. No symptoms questionnaires. No spirometry</td>
</tr>
<tr>
<td>Cook</td>
<td>2013</td>
<td>Urban clinic</td>
<td>11.5</td>
<td>Consecutive recruitment from paediatric Sickle Cell Anaemia Clinic</td>
<td>25</td>
<td>Self-reported respiratory symptoms (ISAAC questionnaire) and spirometry</td>
</tr>
<tr>
<td>Mwalukomo</td>
<td>2016</td>
<td>Urban clinic</td>
<td>11.1</td>
<td>First 3 eligible patients at paediatric HIV clinic per day were recruited</td>
<td>160</td>
<td>Self-reported respiratory symptoms and clinical observation and spirometry</td>
</tr>
<tr>
<td>Leijveld</td>
<td>2017</td>
<td>Urban hospital</td>
<td></td>
<td>Cases: consecutive patients admitted with severe acute malnutrition in 2006–2007. Sibling controls: closest in age to case. Community controls: random direction selected from case home then door-to-door recruitment (age- &amp; sex-matched).</td>
<td>320 cases (of 477 alive 1 year after original discharge); 217 sibling controls; 184 community controls</td>
<td>Spirometry</td>
</tr>
<tr>
<td>Rylance</td>
<td>2019</td>
<td>Rural</td>
<td>7.1</td>
<td>Population sampling with control and intervention arm</td>
<td>804 including 476 (260 intervention and 216 control) from CAPS households</td>
<td>Self-reported respiratory symptoms (BOLD questionnaire) and spirometry</td>
</tr>
<tr>
<td>Fullerton</td>
<td>2011</td>
<td>Rural/urban</td>
<td>39</td>
<td>Cross-sectional survey. Rural: first household semi-randomly selected, then snowballing sampling strategy. Urban: randomly selected from 360 research volunteers, then snowballing sampling strategy. Biased selection toward women</td>
<td>374</td>
<td>Self-reported respiratory symptoms and diagnoses and spirometry.</td>
</tr>
<tr>
<td>To</td>
<td>2012</td>
<td>Rural/urban</td>
<td></td>
<td>Multi-stage cluster design: random</td>
<td>3890</td>
<td>Self-reported respiratory symptoms and diagnoses and self-reported doctor diagnosed.</td>
</tr>
<tr>
<td>Jary</td>
<td>2014</td>
<td>Rural</td>
<td>35</td>
<td>Community based survey of women wishing to purchase a cookstove – not randomly selected.</td>
<td>51</td>
<td>Self-reported respiratory symptoms.</td>
</tr>
<tr>
<td>Meghji (^a)</td>
<td>2016</td>
<td>Urban</td>
<td>42</td>
<td>Random sample from enumerated population – age- and sex-stratified population-representative sample.</td>
<td>1059 (of 1240 eligible)</td>
<td>Self-reported respiratory symptoms (BOLD questionnaire) and spirometry.</td>
</tr>
<tr>
<td>Manjomo</td>
<td>2016</td>
<td>Urban</td>
<td></td>
<td>All patients registered with NCDs attending a chronic care clinic at a primary health care centre.</td>
<td>1135</td>
<td>Diagnosis of asthma at clinic</td>
</tr>
<tr>
<td>Wang</td>
<td>2016</td>
<td>Rural</td>
<td></td>
<td>Cross sectional survey, from three districts. Sampling method unclear. Paediatric adult overlap with participant 10–65 years old.</td>
<td>5643 individuals from 1199 households</td>
<td>Self-reported chronic respiratory symptoms reported as a group</td>
</tr>
<tr>
<td>Banda</td>
<td>2017</td>
<td>Rural</td>
<td>36</td>
<td>Population proportional sampling using electronic satellite maps: 30 villages randomly selected from each cluster (27 health centre catchment population), 7 households randomly selected from each village.</td>
<td>15795 individuals from 6304 households with 1728 who had health passports checked for symptoms</td>
<td>Self-reported respiratory symptoms / health passport assessment of symptoms.</td>
</tr>
<tr>
<td>Das</td>
<td>2017</td>
<td>Rural/peri-urban</td>
<td>37.3</td>
<td>Random sample of households from representative villages.</td>
<td>655 households (382 rural, 273 peri-urban).</td>
<td>Self-reported respiratory symptoms.</td>
</tr>
</tbody>
</table>

\(^a\)From the same study population.
Table 3. Extracted proportions (%) of cases showing symptoms and specific exposures (where reported). Empty cells indicate not reported.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Symptoms (%)</th>
<th>Exposures (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cough</td>
<td>Wheeze</td>
</tr>
<tr>
<td>Paediatric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zverev et al., 2001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cook 2013</td>
<td>41.7</td>
<td>11.2</td>
</tr>
<tr>
<td>Mwalukomo 2016</td>
<td>37.5</td>
<td>8.1</td>
</tr>
<tr>
<td>Leijiveld 2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rylance 2019</td>
<td>8</td>
<td>12.1</td>
</tr>
<tr>
<td>Adult</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fullerton 2011</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>To 2012</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Jary 2014</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td>Meghji 2016&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Manjomo 2016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al., 2016</td>
<td>2.0&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Banda 2017</td>
<td>18.6</td>
<td>5.9</td>
</tr>
<tr>
<td>Das 2017</td>
<td>17.3</td>
<td></td>
</tr>
<tr>
<td>Jary 2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Townend 2017</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Cohen 2019</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nightingale 2019</td>
<td>11.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Secondary analysis from Malawi (pooled data 2019)</td>
<td>10.7</td>
<td>2.2</td>
</tr>
</tbody>
</table>

<sup>a</sup>Open fire for >20 years. <sup>b</sup>Africa region estimate. <sup>c</sup>Chronic symptoms combined. <sup>d</sup>Indoor tobacco/biofuel use. SOB: shortness of breath.

Table 4. Summary extracted spirometry (FEV1, FVC) or obstruction/low FVC where available. Blank cells indicate data that were not reported.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Group/subgroup</th>
<th>Asthma (%)</th>
<th>Low FVC (%)</th>
<th>Obstruction (%)</th>
<th>Reference range</th>
<th>FEV1, L Mean (SD)</th>
<th>FVC, L Mean (SD)</th>
<th>FEV1/FVC % Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatric</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zverev et al 2001</td>
<td>School children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cook 2013</td>
<td>Clinic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>0</td>
<td>Local</td>
<td>1.45 (0.54)</td>
<td>1.68 (0.58)</td>
<td></td>
<td>86 (2.09)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>0</td>
<td>Wang</td>
<td>−1.64&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−1.49&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−0.39&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mwalukomo 2016</td>
<td>Clinic – HIV infected</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>17.9</td>
<td>GLI</td>
<td>−1.31&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−0.89&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−0.27&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>17.2</td>
<td>12.4</td>
<td>Local</td>
<td>92.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>93.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>87.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Leijiveld 2017</td>
<td>Cases – clinic</td>
<td>GLI</td>
<td>−0.47 (1.1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−0.32 (1.0)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−0.21 (0.9)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Controls – siblings</td>
<td>GLI</td>
<td>−0.48 (1.0)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−0.38 (1.1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−0.15 (0.9)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Controls – population</td>
<td>GLI</td>
<td>−0.34 (1.1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−0.15 (1.1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.16 (1.0)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rylance 2019</td>
<td>Intervention</td>
<td>GLI</td>
<td>−0.41 (0.92)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−0.22 (0.77)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−0.4 (0.91)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>GLI</td>
<td>−0.60 (0.97)</td>
<td>−0.44 (0.98)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−0.34 (0.93)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Population</td>
<td>GLI</td>
<td>−0.48 (0.93)</td>
<td>−0.30 (0.96)</td>
<td>−0.03 (0.90)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

https://doi.org/10.4314/mmj.v32i2.3
Discussion

We conducted a systematic review, secondary data analysis, and meta-analysis, of studies relating to non-communicable respiratory disease in Malawi. We identified 17 papers of variable quality with scores on the Newcastle-Ottawa scale ranging from 0 to 7 [15,16,20,22-34]. Five of these studies related to children while 12 of the studies involved adult populations.

In children we found that the main symptom was wheeze, with low FVC being reported in 6.3–20% of the population; obstruction was reported in 7.1–17.9% of the study population [22-26]. In adults, we identified a high burden of lung disease, with cough being the most reported symptom. In studies that used spirometry as an outcome measure, over 40% of the population showed abnormal spirometry results [15,16,20,27]. Low FVC was the most common abnormal spirometry finding, with a pooled population estimate of 37.5% using NHANES Caucasian reference ranges. We also identified a high prevalence of exposure to biomass fuel (50–100%) and a smoking prevalence of 1–21% [27,29,30,34].

Few studies in the published literature have reported chronic respiratory symptoms and spirometry data from sub-Saharan African populations. However, the findings from our present systematic review and meta-analysis, which focussed on Malawi, are consistent with data arising from other sub-Saharan African countries. Data from the ISAAC study sites indicated that wheeze occurs in 5–16% of children in sub-Saharan Africa, with nearly a half of these children exhibiting severe symptoms [11]. On a global basis, wheeze has been reported to occur in 0.8–32.6% of young children (aged 6–7 years and 2.4–37.6% in older children (age 13–14 years) [11]. In adults, cough was the most common symptom described in studies from sub-Saharan Africa; BOLD studies in Nigeria reported a prevalence of cough that was 9.7% [30]. The prevalence of obstruction was lower in Malawi than that found in both Cape Town (19.1%) and in rural Uganda (16.2%), although tobacco smoking was more common in both these populations than in Malawi [13,37]. Two recent studies from Uganda found that the prevalence of obstruction was 2–6.1% and 2% in a rural setting and 1.5% in an urban setting; these figures are more in line with the data highlighted in the present review [18,17].

The high prevalence of low FVC that was evident in Malawi was similar to that seen in Nigeria and other resource-poor settings. However, there is limited a limited body of literature relating to the possible causes of low FVC in adults residing in sub-Saharan Africa [36]. The major strength of this study is that it is the first systematic review and meta-analysis of chronic non-communicable respiratory disease in Malawi and provides a significant enhancement to the growing body of evidence highlighting the high burden of lung disease seen within Malawi and the wider sub-Saharan African region. Our work brings together studies of both paediatric and adult populations from diverse settings in Malawi and includes a secondary analysis of data in order to provide new estimates for the pooled burden of disease. The estimates given within this paper
are, however, limited by inconsistent methodologies. The studies we reported herein were carried out across a range of populations, from the community setting to subgroups within an acute clinic. The paediatric data described herein are particularly limited because only one paediatric study reported lung function in community settings; the other studies related to specific populations, such as children with sickle cell disease. Furthermore, symptoms were not reported in a consistent or standardised manner. Cough, wheeze, exertional dyspnoea, and the production of sputum, were the most common symptoms reported although there was widespread inconsistency in the definitions used for these symptoms. All symptoms were self-reported; in studies without other diagnostic tools, this inevitably reduced the specificity of diagnosis. Diagnosis of COPD and asthma were made using a combination of clinical or self-reported diagnoses and spirometry. This is likely to explain the wide variation seen in categorising the burden of disease in Malawi. All spirometry data were reported in accordance with ATS standards. However, studies used different interpretative strategies with raw FEV1 and FVC being the most common parameters provided for adult populations and Z-scores the most common parameter for the paediatric population. This lack of standardised reporting also created uncertainty with regards to the estimation of disease burden in Malawi and resulted in high heterogeneity with regards to the meta-analysis estimates. As there is no validated reference range for spirometry in sub-Saharan African populations, a variety of reference ranges were used in the studies reported here. The majority of paediatric studies used the Global Lung Function Initiative (GLI) reference ranges while the majority of adult studies used the NHANES Caucasian reference ranges. However, the NHANES Caucasian reference ranges are also known to be associated with limitations, including the potential overestimation of the prevalence of low FVC; however, this reference range does allow for comparison with other studies, including BOLD studies (the largest, multinational study of spirometry findings thus far). Previous studies have also published results that were interpreted with local (unvalidated) reference ranges.

Conclusion

In conclusion, we identified a high burden of chronic respiratory symptoms and abnormal spirometry data (particularly low FVC) in children and adults in Malawi. Estimates for the country-wide burden of disease were limited by the heterogeneity of the methods used to assess symptoms and spirometry. Little is known about the determinants and natural history of non-communicable respiratory disease across the life course in Malawi. We strongly recommend that non-communicable respiratory disease should be a priority for future research in Malawi and that this would benefit from the use of methodologies standardised across studies. For example, it would be particularly useful to standardise diagnostic definitions and report all spirometry data to ATS/ERS standards. A specific consensus on the spirometry reference ranges used, or the development of locally appropriate specific reference ranges, is also needed. The substantial burden of chronic respiratory symptoms and abnormal spirometry data in Malawian children and adults is highly evident in our findings. Consequently, it is vital that we provide high quality, accessible and affordable care to this population, This has implications for Malawian policy- and decision-makers and our efforts to develop universal health coverage in Malawi. Although our systematic review and meta-analysis deliberately focused on Malawi, our findings are of generalisable relevance to the wider sub-Saharan African region.

Authors’ contributions

Design: RN, HJ, JR, KM, ML
Acquisition of data: RN, HJ, ML
Analysis of data: RN, HJ, JM, SR, JR, KM, ML
Interpretation of data: RN, HJ, JM, SR, JM, HC, JR, KM, ML

All of the authors helped to write the manuscript and agreed for the final version to be published. All authors agree to be held accountable for all aspects of the research described herein.

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Conflict of Interests

There are no other conflicts to declare from the authors.

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Section 2: Systematic Review Protocol

Non-communicable lung disease in Malawi across the life course: A SYSTEMATIC REVIEW and meta-analysis
R. Nightingale, H. Jary M. Lesosky, K. Mortimer

Background

Chronic Obstructive Pulmonary Disease (COPD) is estimated to be the third commonest cause of death globally, causing 3 million deaths per year (1, 2): 90% of these deaths occur in low income countries. The Burden of Obstructive Lung Disease (BOLD) Study found an overall moderate to severe COPD prevalence of 19% in Cape Town, South Africa (3). Data for the rest of sub-Saharan Africa are scarce (4), but a more recent Burden of Obstructive Lung Disease (BOLD) study suggest that the prevalence of airflow obstruction in lower income countries in sub-Saharan Africa may be much lower: 6.9% in Blantyre, Malawi and 7.7% in Ile-Ife, Nigeria (5, 6). In addition, a high prevalence of reduced lung volumes (low Forced Vital Capacity (FVC)) has been found in Malawian adults (5, 7, 8). Reduced lung volumes are associated with increased mortality in other settings, even in the absence of respiratory symptoms (9, 10). Low FVC disease predicts mortality better than obstructive disease, and is associated with COPD mortality, indicating that many “COPD” deaths may in fact be due to underlying, undiagnosed low FVC (9).

330 million people worldwide have asthma (11), resulting in 420,000 deaths per year, which is greater than the number of deaths caused globally by malnutrition (2). Data on prevalence amongst adults in sub-Saharan Africa are scarce (estimates range from 3.7% to 15.2%) (12).

There is an absence of data on the prevalence of bronchiectasis in sub-Saharan Africa (in part due to the requirements high income settings for a radiological diagnosis). However, given the multiple respiratory insults – including recurrent infections, tuberculosis, HIV infection and pollution exposure - that many individuals in this setting experience it is anticipated that there is a significant burden of undiagnosed bronchiectasis.

Half the world’s population rely on burning solid fuels for essential household activities, and as a result are exposed to high levels of air pollution inside their homes. In some rural areas, solid fuels are used by up to 100% of the population (13). The World Health Organisation and Global Burden of Disease Study both list exposure to household air pollution (HAP) as a major risk factor for COPD (14, 15). However, two recent large-scale studies pooling high-quality spirometry data from multiple countries found conflicting result regarding the association between HAP and COPD (16, 17). A pooled analysis from 13 low- and middle-income countries found that COPD was 41% more likely in those reporting biomass as their primary source of fuel (Odds ratio 1.41; 95% confidence interval 1.18–1.68) (16). Yet a meta-analysis from 25 countries did not find an association between solid fuel use and airflow obstruction, even when restricted to low- and middle-income countries (17). Recent studies using spirometry from Malawi have also not supported an association (5, 8). Possible explanations for these conflicting findings include possible exposure misclassification due to reliance on self-report biomass use, or residual confounding (for example, due to socioeconomic status) (18).

The reasons for a high prevalence of low FVC amongst adults in parts of sub-Saharan Africa are not well understood, and data does not suggest an association with adult HAP exposures although an association with poverty have been shown (5, 8, 9). Early life (in-utero and childhood) insults, such as HAP exposure, malnutrition and recurrent infections, may play a role in reducing lung growth. Similar lifecourse effects may be replicated in other organ systems, which may be contributing to the increasing burden of other non-communicable diseases (NCDs). For example, early-life insult may reduce nephron numbers or pancreatic mass, which may explain the high burden of hypertension, diabetes and chronic kidney disease that is now widely recognised in sub-Saharan Africa. If this hypothesis is true, NCDs characterised by small organs in low income settings may be phenotypically to NCDs seen in high income settings. The relationship between spirometric abnormalities, other NCDs and exposure to potential insults, such as HAP, across the lifecourse warrants further investigation.
Malawi, one of the world’s poorest countries according to the World Bank, has high rates of solid fuel use and a HIV prevalence of 10.8% (19). In recent years, Malawi has been the focus of several respiratory studies but the available data – spanning both rural and urban populations - has not been analysed together. This review aims to synthesise the current evidence base to quantify the burden of non-communicable lung disease, including COPD, low FVC, asthma and bronchiectasis, amongst Malawian adults, and to explore associations with risk factors (including HAP) and other non-communicable diseases.

Objectives

Primary Objective:

1. To describe the burden of non-communicable lung disease amongst Malawians across the lifecourse.

Secondary Objectives:

1. To identify risk factors for spirometric abnormalities in Malawi.
2. To explore the relationship between exposure to HAP from burning solid fuels and spirometric abnormalities in Malawi.
3. To explore associations between spirometric abnormalities and other non-communicable diseases, including diabetes, chronic kidney disease and hypertension, in Malawian adults.

This systematic review and meta-analysis will consider observational studies (cross-sectional, case-control and cohort studies) and intervention studies related to diagnosis of non-communicable lung disease in Malawi.

Methods

Criteria for considering studies for this review

Types of studies

- Randomised Control Trials, including individually randomised and cluster-randomised studies
- Controlled Before-and-After studies
- Cohort Studies
- Case Control Studies
- Cross-sectional surveys

Types of participants

Individuals of all ages and both sexes from any geographical location within Malawi.

Factors of interest

Non-Communicable LUNG DISEASE

Non-communicable lung disease is the primary condition of interest, including COPD, asthma, low FVC/restrictive disease and bronchiectasis. Only studies that provide data to describe the burden of these conditions will be included. This review will have a special focus on NCLD that has been spirometrically confirmed (for a pooled analysis – see below), but studies describing the burden of these conditions based on diagnosis of symptom will also be included in the narrative synthesis.

The parameters of primary interest are:
• Post Forced Expiratory Volume (FEV\(_1\))
• Forced Vital Capacity (FVC)
• FEV\(_1\):FVC ratio
• % predicted FEV\(_1\)
• % predicted FVC
• % of population with obstructive airways disease
• % of population with restrictive airways disease
• % of population with reversible obstruction

If raw spirometry data is available, Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria will be used to benchmark the spirometry findings.

The secondary parameters of interest are:

• Wheeze
• Shortness of breath
• Chronic cough
• Chronic sputum production

**Household Air Pollution Exposure from solid fuel use**

Exposure to household air pollution from burning solid fuels indoors for household purposes should be quantified in the studies, ideally by direct measurement of air pollution, such as by measurement of specified pollutants (e.g. PM, CO) by household or personal monitoring.

**indicators of other non-communicable diseases**

Other non-communicable diseases of interest include hypertension, diabetes and chronic kidney disease. Data regarding these conditions will be included in this review if objective measure of disease have been made, for example, blood pressure measurement, blood glucose measurement and creatinine measurement.

**Search methods for identification of studies**

**Electronic searches**

The following databases will be searched:

• Cochrane Central Register of Controlled Trials (CENTRAL)
• MEDLINE (1960 to date)
• Scopus (1960 to date) (includes EMBASE)
• Web of Science (1960 to date)
• CINAHL (1960 to date)
• SciELO (1960 to date)

The following inclusion criteria will be applied:

• Human studies

Search terms will be:
Outcomes (OR): “chronic respiratory” OR “non-communicable lung” OR “chronic obstructive pulmonary disease” OR “COPD” OR “asthma” OR “obstructive lung” OR “restrictive lung” OR “obstructive respiratory” OR “restrictive respiratory” OR “obstructive airway*” OR “restrictive airway*” OR “spirometr*” OR “wheeze” OR “chronic cough” OR “shortness of breath” OR “breathlessness” OR “chronic sputum” AND
Location: “Malawi”

Searching other resources
To identify eligible unpublished studies, the following sources will be explored using the same inclusion and exclusion criteria as above:

- www.who.int/trialsearch
- www.clinicaltrials.gov
- EAGLE (European Association for Grey Literature Exploitation)
- Indexes to conference proceedings
- Reference lists from extracted papers and reports
- Contacting researchers in the field and study authors

Data collection and analysis

Database management
EndNote will be used to record the results of the initial searches of each databases. A final merged EndNote library that comprises all the results from each database will be created, with duplicate studies discarded. A note will be kept against each study to indicate the stage at which it is retained or discarded, with the reasons for discarding recorded of discarded at or after the abstract stage.

Selection of studies

- All titles will be reviewed for eligibility by two authors independently
  - At this stage, an inclusive approach will be adopted – studies will only be rejected if the title or abstract unequivocally indicates that the study does not examine relevant exposures or outcomes.
  - Disagreements will be resolved by discussion with a third author
- Abstracts of selected titles will be reviewed for eligibility by two authors independently
  - Disagreements will be resolved by discussion and if no agreement is made, a third author shall be consulted
  - If abstracts for selected titles are not available then a quick review of tables and content of relevant sections will be made to assess eligibility.
- Full text articles of papers of the chosen papers will be reviewed for eligibility, according to exclusion ad exclusion criteria, by two authors independently
  - Disagreements will be resolved by discussion and if no agreement is made, a third author shall be consulted

Data extraction and management
• Data will be extracted using pre-defined data extraction forms (to be piloted on a small subset studies first) by one author.
• The following data will be extracted (dependent on study design):
  o Study Overview
    ▪ Prospective or retrospective
    ▪ Type of study design
    ▪ Location of study
    ▪ Single centre or multi-centre
    ▪ Length of study / follow up period
    ▪ Year of publication
  o Characteristics of Participants
    ▪ Sample selection / recruitment
    ▪ Randomisation and allocation concealment (if appropriate)
    ▪ Number of participants and controls enrolled / randomised
    ▪ Number of participants and controls analysed
    ▪ Reasons for Loss to Follow Up
    ▪ Age range, gender, urban vs rural living
    ▪ Details of sources of smoke/pollution exposure
    ▪ Details of co-morbidities
    ▪ Method of recruitment (eg. Hospital based, community based)
  o Non-communicable Lung Disease
    ▪ Case definitions of COPD/asthma/bronchiectasis/restrictive lung disease
    ▪ Prevalence of COPD
    ▪ Prevalence of asthma
    ▪ Prevalence of bronchiectasis
    ▪ Prevalence of restrictive lung disease
    ▪ Standards using for conducting spirometry
    ▪ Standards used for interpreting spirometry
    ▪ % of participants with acceptable measurements
    ▪ Mean (SD) FEV₁
    ▪ Mean (SD) FVC
    ▪ Mean (SD) % Pred. FEV₁
    ▪ Mean (SD) % Pred. FVC
    ▪ % obstructive disease
    ▪ % restrictive disease
  o Details Household Air Pollution
    ▪ Type of exposure (eg. cooking, heating, lighting)
    ▪ Type of fuel used
    ▪ Household or personal exposure assessment
    ▪ Method of HAP exposure assessment
    ▪ Duration of HAP exposure assessment
    ▪ Mean (SD) PM exposure
    ▪ Mean (SD) CO exposure
  o Other non-communicable diseases
    ▪ Methods used for blood pressure / blood glucose / creatinine measurement
    ▪ Mean (SD) systolic blood pressure
    ▪ Mean (SD) diastolic blood pressure
    ▪ Mean (SD) blood glucose
    ▪ Mean (SD) serum creatinine
  o Details of Intervention (if an intervention study)
    ▪ Type of intervention
    ▪ Duration of intervention
Assessment of Risk of Bias in Included Studies

The risk of bias will be assessed by one author using the Newcastle-Ottawa Scale for assessing risk of bias in observational studies and the Cochrane Collaboration tool for assessing risk of bias in randomised control trials. The risk of bias will be presented in a risk of bias summary table.

Assessment of quality in included studies

Data regarding quality of the study, including review of outcome assessment used, will be extracted using a pre-defined quality appraisal form. Narrative description of study quality, including description of methodology (including case selection or assessment of outcome measures) and analysis (including adjustment for confounders), will be made.

Dealing with missing data

Corresponding authors will be contacted by email or letter, including an explanation of the current review, requesting missing data be provided. In the absence of response, the corresponding author will be contacted again and the rest of the authors will also be contacted.

Assessment of heterogeneity

The heterogeneity of studies, with relation to methodology, populations, and outcomes, will be described. If a sufficient number of studies are identified, then statistical heterogeneity will be assessed using Cochrane’s Q test and I² statistic (I² <50% will be considered sufficient for meta-analysis).

Assessment of reporting biases

If 10 or more studies reporting the same exposures and outcomes are identified, publication bias will be measured using tests for statistical funnel plot asymmetry (Egger’s test and Begg’s tests). If asymmetry is identified, literature searches will be repeated.

Summary Tables

The extracted data and quality assessment information will be entered into a summary table. This will include a quality score, which will be based on assessment of the presence of bias and control of confounding in the study. The table will separate studies using different epidemiological design.

Data synthesis / pooled analysis

- A narrative summary of the findings will be reported according to study design.
- Where raw spirometry data is available for population representative samples, a pooled analysis will be conducted to address the primary and secondary objectives outline above.

References


Appendix for Chapter Six

Section 1: Supplement to Paper

Supplement Tables: Change in pulmonary function and respiratory outcomes in patient treated for pulmonary tuberculosis in Malawi: A longitudinal cohort study

Table 1E GOLD definitions

<table>
<thead>
<tr>
<th>Findings</th>
<th>Spirometric Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-bronchodilator obstruction</td>
<td>FEV1/FVC ratio &lt;0.7</td>
</tr>
<tr>
<td>Post-bronchodilator moderate obstruction</td>
<td>FEV1/FVC ratio &lt;0.7 and FEV1 &lt;80% &amp; FEV1 &gt;50% predicted*</td>
</tr>
<tr>
<td>Post-bronchodilator moderate obstruction</td>
<td>FEV1/FVC ratio &lt;0.7 and FEV1 &lt;50% predicted*</td>
</tr>
<tr>
<td>Spirometric restriction</td>
<td>FEV1/FVC ratio &gt;0.7 and FVC&lt;80% predicted*</td>
</tr>
<tr>
<td>Airway reversibility</td>
<td>FEV1 increase &gt;200ml and &gt;12% following bronchodilator</td>
</tr>
</tbody>
</table>

Predicted values based on age, sex and height referenced to GLI as reported in this study.

Figure 1E Direct acyclic graph (DAG) of variable included in regression models.
Radiological variables were: % abnormal parenchyma, excluding mosaicism (HRCT), At least 1 lobe destroyed (HRCT), Total lung bronchiectasis dilatation severity score (HRCT), Total tree in bud severity score (HRCT), Total lung cavities extent (number score 0-18) (HRCT), Total consolidation score, across whole lung (HRCT), % normal, across whole lung (X-ray), % consolidation, across whole lung (X-ray), Total lung ring & tramline score (X-ray), Pleural effusion (X-ray).
Table 2E: Proportion of participants experiencing clinically relevant improvement, deterioration or change in health markers. Measure between baseline visit and last visit at 3 years (n=309)

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Classification of change</th>
<th>Improvement</th>
<th>No change</th>
<th>Deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>Change ≥1.46kg/m²</td>
<td>106 (36.2%)</td>
<td>168 (57.3%)</td>
<td>19 (6.5%)</td>
</tr>
<tr>
<td></td>
<td>2.79 (2.15-4.34)</td>
<td>0.20 (-0.30-0.80)</td>
<td>-2.04 (-2.77--1.52)</td>
<td></td>
</tr>
<tr>
<td>SGRQ</td>
<td>Change ≥4 units</td>
<td>158 (53.2%)</td>
<td>127 (42.8%)</td>
<td>12 (4.04%)</td>
</tr>
<tr>
<td></td>
<td>-18.17 (-26.53--9.91)</td>
<td>0 (-1.84-0)</td>
<td>17.01 (10.80-19.81)</td>
<td></td>
</tr>
<tr>
<td>6 Minute walk test distance</td>
<td>Change ≥26m</td>
<td>142 (53.6%)</td>
<td>72 (27.2%)</td>
<td>51 (19.3%)</td>
</tr>
<tr>
<td></td>
<td>75.28 (49.95-102.09)</td>
<td>3.48 (-8.23-12.85)</td>
<td>(-85.96-41.23)</td>
<td></td>
</tr>
<tr>
<td>6 minute walk test desaturation (spo2 less 92% at end of walk)</td>
<td>Change “yes” or “no”</td>
<td>14 (5.26%)</td>
<td>248 (93.2%)</td>
<td>4 (1.50%)</td>
</tr>
<tr>
<td>Presence of monthly symptoms</td>
<td>Change between present / absent monthly symptoms</td>
<td>125 (41.5%)</td>
<td>166 (55.2%)</td>
<td>10 (3.3%)</td>
</tr>
<tr>
<td>FEV1 (litres)</td>
<td>Change ≥100ml</td>
<td>88 (35.8%)</td>
<td>85 (34.6%)</td>
<td>73 (29.7%)</td>
</tr>
<tr>
<td></td>
<td>0.21 (0.15-0.31)</td>
<td>0 (-0.04-0.06)</td>
<td>-0.18 (-0.31- -0.14)</td>
<td></td>
</tr>
<tr>
<td>FVC (litres)</td>
<td>Change ≥100ml</td>
<td>126 (51.2%)</td>
<td>68 (27.6%)</td>
<td>52 (21.1%)</td>
</tr>
<tr>
<td></td>
<td>0.25 (0.17-0.42)</td>
<td>0 (-0.03-0.05)</td>
<td>-0.25 (-0.34--0.15)</td>
<td></td>
</tr>
<tr>
<td>Unscheduled visit to healthcare for respiratory condition</td>
<td>Change ≥1 visit</td>
<td>46 (15.4%)</td>
<td>246 (82.3%)</td>
<td>7 (2.3%)</td>
</tr>
<tr>
<td></td>
<td>-1 (-1 -1)</td>
<td>0 (-0)</td>
<td>2 (2-2)</td>
<td></td>
</tr>
</tbody>
</table>

*All continuous variable normalised to time (1095 days since baseline measurements) $Matched post bronchodilator spirometry to ATS standards n=246

Table 3E: Mixed effect regression model, investigating spirometry values in the three year follow up period after TB treatment completion

<table>
<thead>
<tr>
<th>Variable measured at TB treatment completion</th>
<th>Multivariate model no radiology</th>
<th>Multivariate model (HRCT)</th>
<th>Multivariate model (X-ray)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z-score FEV1 over three follow up period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since visits (days)</td>
<td>0.04 (0.03-0.06)*</td>
<td>0.04 (0.03-0.06)*</td>
<td>0.04 (0.03-0.06)*</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.11 (-0.02-0.23)</td>
<td>0.15 (0.03-0.26)*</td>
<td>0.11 (-0.01-0.23)</td>
</tr>
<tr>
<td>Gender male</td>
<td>0.44 (0.14-0.74)*</td>
<td>0.53 (0.25-0.80)*</td>
<td>0.48 (0.20-0.76)*</td>
</tr>
<tr>
<td>Microbiological diagnosed TB</td>
<td>0.10 (-0.21-0.41)</td>
<td>0.11 (-0.17-0.29)</td>
<td>0.080 (-0.21-0.37)</td>
</tr>
<tr>
<td>HIV positive status</td>
<td>0.38 (0.12-0.64)*</td>
<td>0.20 (-0.04-0.44)</td>
<td>0.22 (-0.03-0.47)</td>
</tr>
<tr>
<td>History of past respiratory illness</td>
<td>-0.24 (-0.48-0.01)</td>
<td>-0.23 (-0.45- -0.01)*</td>
<td>-0.24 (-2.03- -0.47)</td>
</tr>
<tr>
<td>Urban SES quintile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-2nd poorest</td>
<td>0.20 (-0.33-0.74)</td>
<td>0.23 (-0.26-0.73)</td>
<td>0.20 (-2.03- -0.47)</td>
</tr>
<tr>
<td>-Middle</td>
<td>0.16 (-0.39-0.70)</td>
<td>0.11 (-0.39-0.61)</td>
<td>0.18 (-0.33-0.68)</td>
</tr>
<tr>
<td>-2nd most wealthy</td>
<td>0.46 (-0.08-1.01)</td>
<td>0.33 (-0.17-0.83)</td>
<td>0.39 (-0.11-0.89)</td>
</tr>
<tr>
<td>-Most wealthy</td>
<td>0.51 (-0.08-1.10)</td>
<td>0.40 (-0.14-0.94)</td>
<td>0.41 (-0.14-0.96)</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>-0.14 (-0.44-0.17)</td>
<td>0.08 (-0.20-0.36)</td>
<td>0.03 (-0.25-0.32)</td>
</tr>
<tr>
<td>BMI (K/m2)</td>
<td>0.21 (0.08-0.34)*</td>
<td>0.09 (-0.03-2.11)</td>
<td>0.12 (-0.01-0.24)</td>
</tr>
<tr>
<td>Unscheduled respiratory visits</td>
<td>-0.12 (-0.37-0.13)</td>
<td>-0.04 (-0.25-0.19)</td>
<td>0.01(-0.22-0.24)</td>
</tr>
<tr>
<td>Duration of illness pre-diagnosis</td>
<td>-0.16 (-0.29--0.03)*</td>
<td>-0.13 (-0.24--0.01)*</td>
<td>-0.13 (-0.23--0.01)*</td>
</tr>
<tr>
<td>% abnormal parenchyma, excluding mosaicism (HRCT)</td>
<td></td>
<td>-0.00 (-0.00--0.00)*</td>
<td></td>
</tr>
<tr>
<td>At least 1 lobe destroyed (HRCT)</td>
<td>-0.11 (-0.52-0.29)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4E: Linear regression model, investigating absolute change in spirometry values in the three year follow up period after TB treatment completion

<table>
<thead>
<tr>
<th>Variable measured at TB treatment completion</th>
<th>Multivariate model no radiology</th>
<th>Multivariate model (HRCT)</th>
<th>Multivariate model (X-ray)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in absolute FEV1 (L) from baseline to year three (negative is worsening FEV1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.006 (-0.009--0.003)*</td>
<td>-0.006 (-0.009--0.003)*</td>
<td>-0.005 (-0.0089--0.003)*</td>
</tr>
<tr>
<td>Gender male</td>
<td>0.063 (-0.013-0.140)</td>
<td>0.06 (-0.157-0.138)</td>
<td>0.051 (-0.23-0.125)</td>
</tr>
<tr>
<td>Microbiological diagnosed TB</td>
<td>-0.002 (-0.080-0.76)</td>
<td>-0.009 (-0.874-0.069)</td>
<td>0.004 (-0.071-0.079)</td>
</tr>
<tr>
<td>HIV positive status</td>
<td>0.083 (0.017-0.150)*</td>
<td>0.093 (0.027-0.160)*</td>
<td>0.103 (0.037-0.128)*</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------------</td>
<td>----------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>History of past respiratory illness</td>
<td>0.056 (-0.004-0.118)</td>
<td>0.061 (0.001-0.123)</td>
<td>0.040 (-0.020-0.100)</td>
</tr>
<tr>
<td>Urban SES quintile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-2nd poorest</td>
<td>-0.029 (-0.172-0.113)</td>
<td>-0.012 (-0.154-0.129)</td>
<td>-0.006 (-0.144-0.131)</td>
</tr>
<tr>
<td>-Middle</td>
<td>0.006 (-0.140-0.150)</td>
<td>0.22 (-0.123-0.168)</td>
<td>0.028 (-0.112-0.168)</td>
</tr>
<tr>
<td>-2nd most wealthy</td>
<td>-0.039 (-0.186-0.107)</td>
<td>-0.008 (-0.156-0.140)</td>
<td>0.001 (-0.141-0.142)</td>
</tr>
<tr>
<td>-Most wealthy</td>
<td>-0.071 (-0.231-0.087)</td>
<td>-0.049 (-0.209-0.110)</td>
<td>-0.026 (-0.180-0.128)</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>0.034 (-0.043-0.11)</td>
<td>0.008 (-0.070-0.087)</td>
<td>0.04 (-0.04-0.115)</td>
</tr>
<tr>
<td>BMI (K/m2)</td>
<td>-0.003 (-0.133-0.008)</td>
<td>-0.001 (-0.011-0.011)</td>
<td>-0.003 (-0.013-0.008)</td>
</tr>
<tr>
<td>Unscheduled respiratory visits</td>
<td>-0.007 (-0.061-0.465)</td>
<td>-0.027 (-0.082-0.286)</td>
<td>-0.028 (-0.081-0.026)</td>
</tr>
<tr>
<td>Duration of illness pre-diagnosis</td>
<td>0.000 (-0.000-0.000)</td>
<td>0.000 (-0.000-0.000)</td>
<td>0.000 (-0.000-0.000)</td>
</tr>
<tr>
<td>% abnormal parenchyma, excluding mosaicism (HRCT)</td>
<td>0.000 (-0.000-0.000)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 1 lobe destroyed (HRCT)</td>
<td>-0.047 (-0.162-0.684)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total lung bronchiectasis dilatation severity score (HRCT)</td>
<td>0.112 (-0.017-0.039)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total tree in bud severity score (HRCT)</td>
<td>0.006 (-0.004-0.016)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total lung cavities extent/number score (HRCT)</td>
<td>0.003 (-0.015-0.020)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total consolidation score, across whole lung (HRCT)</td>
<td>0.002 (-0.001-0.004)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% normal, across whole lung (X-ray)</td>
<td></td>
<td>-0.001 (-0.007-0.004)</td>
<td></td>
</tr>
<tr>
<td>% consolidation, across whole lung (X-ray)</td>
<td></td>
<td>0.010 (-0.001-0.021)</td>
<td></td>
</tr>
<tr>
<td>Total lung ring &amp; tramline score (X-ray)</td>
<td></td>
<td>-0.003 (-0.019-0.013)</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion (X-ray)</td>
<td></td>
<td>0.160 (0.016-0.304)</td>
<td></td>
</tr>
</tbody>
</table>

**Difference in absolute FVC (L) from baseline to year three (negative is worsening FVC)**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>-0.007 (-0.010--0.004)*</th>
<th>-0.007 (-0.011--0.004)*</th>
<th>-0.007 (-0.010--0.033)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender male</td>
<td>0.107 (0.213-0.192)*</td>
<td>0.112 (0.030-0.194)*</td>
<td>0.089 (0.009-0.170)*</td>
</tr>
<tr>
<td>Microbiological diagnosed TB</td>
<td>0.037 (-0.51-0.124)</td>
<td>0.036 (-0.048-0.120)</td>
<td>0.046 (-0.037-0.127)</td>
</tr>
<tr>
<td>HIV positive status</td>
<td>0.104 (0.030-0.180)*</td>
<td>0.128 (0.056-0.200)*</td>
<td>0.133 (0.063-0.202)*</td>
</tr>
<tr>
<td>History of past respiratory illness</td>
<td>0.049 (-0.020-0.119)</td>
<td>0.553 (-0.010-0.121)</td>
<td>0.035 (-0.031-0.101)</td>
</tr>
<tr>
<td>Urban SES quintile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-2nd poorest</td>
<td>0.016 (-0.144-0.177)</td>
<td>0.042 (-0.109-0.195)</td>
<td>0.056 (-0.093-0.205)</td>
</tr>
<tr>
<td>-Middle</td>
<td>0.030 (-0.134-0.193)</td>
<td>0.045 (-0.111-0.202)</td>
<td>0.057 (-0.09-0.208)</td>
</tr>
<tr>
<td>-2nd most wealthy</td>
<td>-0.018 (-0.183-0.146)</td>
<td>0.022 (-0.137-0.181)</td>
<td>0.036 (-0.118-0.189)</td>
</tr>
<tr>
<td>-Most wealthy</td>
<td>-0.041 (-0.220-0.137)</td>
<td>-0.011 (-0.183-0.160)</td>
<td>0.029 (-0.137-0.195)</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>0.103 (0.017-0.190)*</td>
<td>0.055 (-0.028-0.139)</td>
<td>0.104 (0.022-0.186)*</td>
</tr>
<tr>
<td>BMI (K/m2)</td>
<td>-0.006 (-0.018-0.006)</td>
<td>0.001 (-0.011-0.127)</td>
<td>-0.004 (-0.160-0.007)</td>
</tr>
<tr>
<td>Unscheduled respiratory visits</td>
<td>0.014 (-0.046-0.076)</td>
<td>-0.019 (-0.079-0.040)</td>
<td>-0.022 (-0.080-0.035)</td>
</tr>
<tr>
<td>Duration of illness pre-diagnosis</td>
<td>0.000 (-0.000-0.000)</td>
<td>0.000 (-0.000-0.000)</td>
<td>-0.000 (-0.000-0.000)</td>
</tr>
<tr>
<td>% abnormal parenchyma, excluding mosaicism (HRCT)</td>
<td>0.000 (-0.000-0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 1 lobe destroyed (HRCT)</td>
<td>0.047 (-0.077-0.171)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total lung bronchiectasis dilatation severity score (HRCT)</td>
<td>0.007 (-0.23-0.037)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total tree in bud severity score (HRCT)</td>
<td>0.013 (0.002-0.024)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total lung cavities extent/number score (HRCT)</td>
<td>0.005 (-0.014-0.024)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total consolidation score, across whole lung (HRCT)</td>
<td>0.004 (0.001-0.006)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% normal, across whole lung (X-ray)</td>
<td></td>
<td>-0.004 (-0.010-0.002)</td>
<td></td>
</tr>
<tr>
<td>% consolidation, across whole lung (X-ray)</td>
<td></td>
<td>0.016 (0.004-0.028)*</td>
<td></td>
</tr>
<tr>
<td>Total lung ring &amp; tramline score (X-ray)</td>
<td></td>
<td>-0.007 (-0.024-0.010)</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion (X-ray)</td>
<td></td>
<td>0.180 (0.024-0.337)*</td>
<td></td>
</tr>
</tbody>
</table>
Table 5E: Linear regression model, investigating Z-score change in spirometry values in the three year follow up period after TB treatment completion

<table>
<thead>
<tr>
<th>Variable measured at TB treatment completion</th>
<th>Multivariate model no radiology</th>
<th>Multivariate model (HRCT)</th>
<th>Multivariate model (X-ray)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in Z-score FEV1 (L) from baseline to year three (negative is worsening FEV1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.011 (-0.02 - 0.01)*</td>
<td>-0.01 (-0.02 - 0.01)*</td>
<td>-0.01 (-0.02 - 0.00)</td>
</tr>
<tr>
<td>Gender male</td>
<td>0.09 (-0.09-0.28)</td>
<td>0.08 (-0.11-0.26)</td>
<td>0.06 (-0.13-0.24)</td>
</tr>
<tr>
<td>Microbiological diagnosed TB</td>
<td>-0.03 (-0.23-0.16)</td>
<td>-0.062 (-0.25-0.13)</td>
<td>-0.02 (-0.21-0.16)</td>
</tr>
<tr>
<td>HIV positive status</td>
<td>0.19 (0.02-0.16)*</td>
<td>0.21 (0.05-0.37)*</td>
<td>0.24 (0.07-0.39)*</td>
</tr>
<tr>
<td>History of past respiratory illness</td>
<td>0.14 (-0.01-0.29)</td>
<td>0.15 (0.01-0.299)*</td>
<td>0.09 (-0.06-0.24)</td>
</tr>
<tr>
<td>Urban SES quintile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd poorest</td>
<td>-0.07 (-0.42-0.27)</td>
<td>-0.3 (-0.37-0.32)</td>
<td>-0.01 (-0.35-0.32)</td>
</tr>
<tr>
<td>Middle</td>
<td>0.00 (-0.35-0.35)</td>
<td>0.7 (-0.28-0.42)</td>
<td>0.07 (-0.28-0.41)</td>
</tr>
<tr>
<td>Most wealthy</td>
<td>-0.07 (-0.43-0.29)</td>
<td>0.02 (-0.34-0.38)</td>
<td>0.03 (-0.32-0.37)</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>0.10 (-0.09-0.29)</td>
<td>0.04 (-0.151-0.23)</td>
<td>0.12 (-0.8-0.29)</td>
</tr>
<tr>
<td>BMI (K/m2)</td>
<td>-0.00 (-0.03-0.02)</td>
<td>0.00 (-0.02-0.03)</td>
<td>-0.00 (-0.3-0.3)</td>
</tr>
<tr>
<td>Unscheduled respiratory visits</td>
<td>-0.04 (-0.18-0.09)</td>
<td>-0.09 (-0.22-0.04)</td>
<td>-0.08 (-0.22-0.05)</td>
</tr>
<tr>
<td>Duration of illness pre-diagnosis</td>
<td>0.00 (-0.00-0.00)</td>
<td>0.00 (-0.00-0.00)</td>
<td>0.00 (-0.00-0.00)</td>
</tr>
<tr>
<td>% abnormal parenchyma, excluding mosaicism (HRCT)</td>
<td>0.00 (0.00-0.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 1 lobe destroyed (HRCT)</td>
<td></td>
<td>-0.19 (-0.47-0.08)</td>
<td></td>
</tr>
<tr>
<td>Total lung bronchiectasis dilatation severity score (HRCT)</td>
<td></td>
<td>0.02 (-0.5-0.09)</td>
<td></td>
</tr>
<tr>
<td>Total tree in bud severity score (HRCT)</td>
<td></td>
<td>0.02 (-0.01-0.04)</td>
<td></td>
</tr>
<tr>
<td>Total lung cavities extent/number score (HRCT)</td>
<td></td>
<td>-0.00 (-0.04-0.04)</td>
<td></td>
</tr>
<tr>
<td>Total consolidation score, across whole lung (HRCT)</td>
<td></td>
<td>0.01 (-0.01-0.01)</td>
<td></td>
</tr>
<tr>
<td>% normal, across whole lung (X-ray)</td>
<td></td>
<td></td>
<td>0.00 (-0.012-0.14)</td>
</tr>
<tr>
<td>% consolidation, across whole lung (X-ray)</td>
<td></td>
<td></td>
<td>0.03 (0.01-0.06)*</td>
</tr>
<tr>
<td>Total lung ring &amp; tramline score (X-ray)</td>
<td></td>
<td></td>
<td>0.00 (-0.04-0.4)</td>
</tr>
<tr>
<td>Pleural effusion (X-ray)</td>
<td></td>
<td></td>
<td>0.42 (0.07-0.77)*</td>
</tr>
<tr>
<td>Difference in Z-score FVC (L) from baseline to year three (negative is worsening FVC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.01 (-0.02---0.00)*</td>
<td>-0.01 (-0.02 - 0.01)*</td>
<td>-0.01 (-0.02 - 0.00)*</td>
</tr>
<tr>
<td>Gender male</td>
<td>0.13 (-0.07-0.33)</td>
<td>0.13 (-0.05-0.31)</td>
<td>0.08 (-0.10-0.26)</td>
</tr>
<tr>
<td>Microbiological diagnosed TB</td>
<td>0.07 (-0.13-0.28)</td>
<td>0.07 (-0.12-0.25)</td>
<td>0.09 (-0.09-0.27)</td>
</tr>
<tr>
<td>HIV positive status</td>
<td>0.18 (0.01-0.35)*</td>
<td>0.23 (0.71-0.40)*</td>
<td>0.24 (0.09-0.40)*</td>
</tr>
<tr>
<td>History of past respiratory illness</td>
<td>0.15 (-0.01-0.31)</td>
<td>0.17 (0.02-0.31)</td>
<td>0.13 (-0.21-0.27)</td>
</tr>
<tr>
<td>Urban SES quintile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd poorest</td>
<td>-0.00 (-0.37-0.37)</td>
<td>0.06 (-0.28-0.40)</td>
<td>0.10 (-0.23-0.44)</td>
</tr>
<tr>
<td>Middle</td>
<td>-0.01 (-0.38-0.36)</td>
<td>0.04 (-0.31-0.39)</td>
<td>0.06 (-0.28-0.40)</td>
</tr>
<tr>
<td>Most wealthy</td>
<td>-0.04 (-0.42-0.33)</td>
<td>0.61 (-0.30-0.42)</td>
<td>0.09 (-0.25-0.44)</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>0.23 (0.03-0.43)*</td>
<td>0.12 (-0.07-0.31)</td>
<td>0.22 (0.04-0.41)</td>
</tr>
<tr>
<td>BMI (K/m2)</td>
<td>-0.01 (-0.4-0.01)</td>
<td>0.00 (-0.02-0.03)</td>
<td>-0.01 (-0.04-0.02)</td>
</tr>
<tr>
<td>Unscheduled respiratory visits</td>
<td>0.01 (-0.13-0.14)</td>
<td>-0.07 (-0.21-0.06)</td>
<td>-0.08 (-0.21-0.05)</td>
</tr>
<tr>
<td>Duration of illness pre-diagnosis</td>
<td>-0.00 (-0.00-0.00)</td>
<td>0.00 (-0.00-0.00)</td>
<td>-0.00 (-0.00-0.00)</td>
</tr>
<tr>
<td>% abnormal parenchyma, excluding mosaicism (HRCT)</td>
<td>0.00 (-0.00-0.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 1 lobe destroyed (HRCT)</td>
<td>0.103 (-0.18-0.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total lung bronchiectasis dilatation severity score (HRCT)</td>
<td>0.00 (-0.07-0.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total tree in bud severity score (HRCT)</td>
<td>0.03 (0.00-0.50)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td>Total lung cavities extent/number score (HRCT)</td>
<td>0.01 (-0.4-0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total consolidation score, across whole lung (HRCT)</td>
<td>0.01 (0.00-0.01)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% normal, across whole lung (X-ray)</td>
<td>-0.01 (-0.02-0.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% consolidation, across whole lung (X-ray)</td>
<td>0.05 (0.02-0.07)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total lung ring &amp; tramline score (X-ray)</td>
<td>-0.02 (-0.06-0.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural effusion (X-ray)</td>
<td>0.39 (0.04-0.74)*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table four derived question extended footnote**

Over the past 3-months I have (had shortness of breath / coughed / brought up sputum / had attacks of wheezing): not at all / only with chest infections / a few days a month / several days a week / most days a week; If you have tried to work in the past 3-months: my chest trouble does not affect my work / my chest trouble interferes with my work or made me change my work / my chest trouble made me stop work; Which of these statements best describes how your chest affects you: It does not stop me doing anything I would like to do / It stops me doing 1-2 things I would like to do / it stops me doing most of the things I would like to do / It stops me doing everything I would like to do.
Section 2: Ethics Application Form

GOVERNANCE & ETHICS APPLICATION FORM

Please refer closely to the Guidance Notes when completing this form.
Please ensure that this form is completed fully and the relevant enclosures are received, so that the study can be properly reviewed by the Research Ethics Committee. If any documentation is missing, proposals will not be submitted for review.

<table>
<thead>
<tr>
<th>Please confirm that this application is for:</th>
<th>YES</th>
<th>NO</th>
<th>Does your study require Sponsorship Approval only (i.e. NHS studies)? If yes, do not complete this form. Complete GOVTEM001 Sponsorship &amp; Indemnity Form, which does not include REC-specific questions.</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSTM Sponsorship Approval</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSTM REC Approval</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*If the Sponsor is not LSTM, provide documents which confirm Sponsorship

Project Title: Life after Tuberculosis 2 (LAT2): Among patients with post TB lung disease, how does severity and progression predict healthcare seeking and treatment?

Applicant Full Name: Mrs Rebecca Nightingale

Email address: Rebecca.nightingale@lstmed.ac.uk

Postal Address (If not LSTM): LSTM.

Telephone number: 07702812183 (personal number)

Administrative Contact Name: n/a

Administrative Contact Email: n/a

Budget & Administration Charges
An administration charge of £250 for awards of over £10,000 and £50 for those below will be made for ethical approval

Is the proposed work already funded? Yes

Total budget of proposal £121,972 Name of Funder MRC/NIHR

Main Applicant and Research Team
List LSTM research team and all collaborators.
(Please include all overseas collaborators and give their affiliations, qualifications and role in the study).

<table>
<thead>
<tr>
<th>Name</th>
<th>Organisation</th>
<th>Qualifications</th>
<th>Role in Study</th>
<th>Geographic Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebecca Nightingale</td>
<td>LSTM/MLW</td>
<td>Bsc, MCSP, MSc, MRes</td>
<td>Primary investigator/PhD Student</td>
<td>LSTM, Liverpool/Blantyre Malawi</td>
</tr>
<tr>
<td>Dr Jamie Rylance</td>
<td>LSTM/MLW</td>
<td>BMedSci, BMBS, MRCP, DTM&amp;H, PhD</td>
<td>Primary PhD supervisor/ Primary co-investigator</td>
<td>Blantyre, Malawi</td>
</tr>
<tr>
<td>Name</td>
<td>Institution</td>
<td>Qualifications</td>
<td>Role</td>
<td>Location</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------</td>
<td>----------------</td>
<td>-------------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Dr Kevin Mortimer</td>
<td>LSTM</td>
<td>BA MA MB BChir FRCP DTM&amp;H MSc PhD</td>
<td>PhD Supervisor/Co-investigator</td>
<td>LSTM, Liverpool, UK</td>
</tr>
<tr>
<td>Prof Bertie Squire</td>
<td>LSTM</td>
<td>BSC, MB BChir, MD (Research), FRCP</td>
<td>PhD supervisor/Co-Investigator</td>
<td>LSTM, Liverpool, UK</td>
</tr>
<tr>
<td>Dr Emanuele Giorgi</td>
<td>Lancaster University</td>
<td>Bsc, MSc, PhD</td>
<td>PhD supervisor/Biostatistics, Co-Investigator</td>
<td>Lancaster, UK</td>
</tr>
<tr>
<td>Dr Peter Banda</td>
<td>The College of Medicine, University of Malawi</td>
<td>Medical Doctor</td>
<td>Co-investigator</td>
<td>Blantyre, Malawi</td>
</tr>
<tr>
<td>Dr Jamilah Meghji</td>
<td>LSTM/MLW</td>
<td>BA, BM, B.Ch. Master of Public Health</td>
<td>Co-Investigator</td>
<td>Blantyre, Malawi</td>
</tr>
</tbody>
</table>
## Project Details

<table>
<thead>
<tr>
<th>Proposed start date</th>
<th>Proposed end date</th>
<th>Total number of participants (refer to A.5)</th>
<th>Is the study multi-centre?</th>
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</thead>
<tbody>
<tr>
<td>01/04/2018</td>
<td>30/08/2020</td>
<td>400</td>
<td>No</td>
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</tbody>
</table>
### Type of Research

What type of research project is it?

Please indicate yes or no to each question and mark all that apply:

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Trial**

1. Involve a novel investigational drug or device
2. Involve a licensed drug or device

**Human Tissue Study**

3. Involve the collection of samples of human blood, bodily secretions or tissue
4. Involve collection and / or storage of human tissue samples on LSTM premises
5. Involve use of human tissue stored in a tissue bank or previously collected from consenting individuals (i.e. in a separate research study)
6. Human tissue collected in any other context

**Human Contact Study**

7. Involve any form of quantitative or qualitative methods
8. Vector studies involving human participants
9. Involve exposing humans to an existing or modified non-medicinal intervention, training or process, including a new system

**Data Study**

10. Data from patient records or public health surveillance (does not require consent)
11. Data collected during a separate research study (does require consent)

Other, please specify:

---

### In-Country / Other Ethical Approval

Please list the country(ies) where the research will be carried out and the status of in-country ethical approval

Add additional lines as necessary

<table>
<thead>
<tr>
<th>Country</th>
<th>Received</th>
<th>Pending</th>
<th>Not Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malawi</td>
<td>X</td>
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<td></td>
</tr>
<tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Have you submitted this proposal to any other Research Ethics Committees not named above?

If yes, please state name of institution:

1. No

All correspondence from partner institutions must reference the same study title as indicated on this application.

Please note if you have marked ‘Not Required’ for any country above, WRITTEN EVIDENCE must be provided to confirm that in-country ethical approval is not required. This evidence should be attached as an annex to the application. Acceptable evidence includes:

- a letter from the national Ministry of Health or other relevant regulatory authority
- a letter from an authorised signatory at a local partner

A letter from a co-investigator or other researcher at a local partner institution is NOT sufficient evidence. Your ethics application will not be considered until evidence is provided.

Have you submitted this proposal to the LSTM Research Ethics Committee before?

<table>
<thead>
<tr>
<th>No</th>
<th>If ‘YES’, please give date of previous review</th>
</tr>
</thead>
</table>

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GLOSSARY OF TERMS
Please provide a list of specialist or scientific acronyms used in the application with their full name and any relevant explanation that would be helpful to committee members that may not be an expert in your area of work.
Please limit this list to 10 acronyms.
TB  Tuberculosis
PTB Pulmonary tuberculosis
COMREC College of medicine research and ethics committee
MLW Malawi Liverpool Wellcome (Trust Research Programme)
LAT Life after pulmonary tuberculosis study

SECTION A
STUDY OUTLINE
A.1 LAY SUMMARY: Please use simple language which is understandable to a non-scientific/non-academic audience. This section must not exceed 300 words. Clearly define problem, methods and use of outputs.
This project focuses on patients after they have finished treatment for Pulmonary Tuberculosis (PTB). These patients often experience symptoms, such as coughing, despite having been successfully treated. It is not known how many patients have these symptoms or how it affects them. They maybe treated again for PTB unnecessarily. This is an unnecessary cost for the hospital and patients receive powerful drugs that they may not need. This research will investigate how many people have these symptoms, get repeat treatment, and how it affects them. If many patients have symptoms, methods of treating the lingering lung disease, could be used to improve the patient’s life and reduce the burden on the hospital
The study will follow up an already well-defined group of patients based in Blantyre, Malawi. They have already been followed up for a year after treatment for their PTB. This study will follow them for a further 2 years. They will have data collected on their lung function (spirometry), their clinical presentation (such as oxygen levels), their functional ability (such as how far they walk in 6 minutes), their symptoms, how often they have accessed health care and the economic impact of any post TB symptoms. Data will be collected using questionnaires, after consent data from the previous study (LAT) will be included, data will also be sourced from the participants health records.
Participants will be followed in person every 6 months and have an extra contact every 3 month (ideally via the telephone).

A.2 JUSTIFICATION FOR THE RESEARCH: Give a brief explanation of the importance of the research to be conducted. What needs will it address and how will it build on previous research? (max 300 words)
Based on existing evidence, this project hypothesises that patients who have been treated for PTB will suffer significant ventilatory abnormalities that may impact their quality of life. They are likely to need access to further acute care and may be retreated for TB based on their symptoms alone. This will impact them as individuals, as well as the wider healthcare system.
This project will allow for continued follow-up of a cohort of PTB patients. If the prevalence and severity of post-TB lung disease over a 3-year period (1st year already defined) can be established in this cohort, it will assist in defining a quality care pathway for post-PTB patients that is applicable in low-income countries.
The project also aims to identify opportunities for optimising the management of post-PTB lung disease to minimise symptom burdens and limit lung function decline. This will be done through the current clinics at Blantyre’s Queen Elizabeth Hospital (QECH). For example, if the patients have significant sputum and bronchiectasis symptoms, simple chest physio may be a cheap and accessible solution. Once this study is complete, an interventional study will be designed to establish the best treatment options. This cannot be done until accurate phenotyping and clinical presentations and patterns are established, which this study will achieve.
The study also aims to provide evidence of the need for a further longitudinal study investigating the outcomes of PTB over a longer period. There is potential for this cohort to continue their follow-up for 5 -10 years.
Giving clinicians the evidence base to change patient care pathways will have a significant impact on the quality of treatment given to both the individual and wider patient groups.

A.3 OBJECTIVES: List the major objectives of the study. These must be achievable by the proposed design and methods. Please list the key outcome measure for each objective. *(max 300 words)*

The overall aim of the research is to improve our understanding of chronic lung disease in Malawian adults with a focus on post-tuberculosis lung disease.

Specific

1. To determine the prevalence and severity of chronic respiratory symptoms, measured by spirometric change and clinical features, 2-4 years from initial episode of PTB in Blantyre, Malawi.
   **Key Outcome:** Spirometry change over change.

2. To determine the relationship between severity of chronic respiratory symptoms and acute health care usage and repeated TB treatment, determined by questionnaire data, clinical data and following the participant’s healthcare seeking behaviours.
   **Key Outcome:** Relationships between spirometry data, clinical data and questionnaire data asking about acute health access and impact of TB.

3. To validate and test, exposure, energy, smoking, Post-TB lung disease and symptoms questionnaires within a post-TB population.
   **Key outcome:** Use of newly designed questionnaires as part of the questionnaire data collection.

A.4 METHODOLOGY: Please include the methodology for each objective (if different) and justify the rationale behind the use of the chosen methodology. Please use simple language which is clear to a non-scientific/non-academic audience. Please keep this section concise and ensure that specialist terms are explained. *(max. 1000 words)*

This is a longitudinal study of the prevalence and determinants of non-communicable lung disease in post-TB adults, including the measurement of lung function and health seeking behaviours. This study will follow a cohort of post-TB lung patients 2-4 years after they have finished treatment.

**Study Location**

Adults will be recruited from referrals made to the post-TB chest clinic at Queen Elizabeth Central Hospital, Blantyre, Malawi, which is led by Dr Peter Banda (consultant respiratory physician). Data will be collected within Queen Elizabeth Central Hospital or in the home setting if participants are unable to attend the hospital.

**Study population**

Participants will be consenting adults (over the age of 15) who have been referred from the LAT study to the post-TB chest clinics in Queen Elizabeth Hospital.

**Data collection**
Participants will only be recruited if they give informed consent and if they decline it will not affect their routine care. Participants will be followed up in person every 6 months at Queen Elizabeth Hospital Blantyre or in their home setting if they are unable to come to come to hospital. A telephone call every 3 months will be conducted by field staff to maintain contact with participants and monitor the participants and their healthcare seeking.

Study methods will involve:

1. A questionnaire about respiratory symptoms (including questions from the standardised St George’s respiratory questionnaire) and healthcare access (including a record of their health passport), administered by study staff in Chichewa or English.
2. A breathing test called spirometry (widely used non-invasive test of lung function).
3. 6-minute walk test (a standard test to measure functional ability in patient with lung disease).
4. Clinical measures including Oxygen saturation and Respiratory rate.
5. Comparison of previous spirometry, questionnaire data and clinical outcomes done as part of the ‘Life after TB’ study (LAT).
6. If participants have symptoms of TB they will be referred to hospital for further investigation and management.

These study methods are already in place and being used by the ‘Life after pulmonary TB’ study. They have worked in Malawi before and are well accepted by participants.

**Detailed data collection information**

**Clinical Measurements**

Measurements of height, weight, oxygen saturations, respiratory rate and a 6 minute walk test will be collected by study staff using standardised procedures.

**Spirometry**

Spirometry will be performed according to ATS/ERS guidelines using a new diagnostic design (ndd) Easy on-PC spirometer or Easy-one spirometer in the Queen Elizabeth Hospital or the participant’s home if they can’t attend the hospital. Spirometry will be performed before and after 4 puffs (total 400 micrograms) of a Salbutamol inhaler via a large volume spacer. The participant will blow into the machine a maximum of 8 times, to record the maximum lung volume (FVC) and amount of air expired in the first second (FEV1). All study staff completing spirometry will have a spirometry competence certificate from the Pan African Thoracic society or equivalent international recognised qualification, or have been trained in spirometry as part of their professional qualifications.

**Questionnaire**

The questionnaires will be administered every 6 months by the study staff in English or Chichewa, including questions from the St Georges questionnaire and questions about health seeking behaviours and a record of their health passport. The participants will be asked about respiratory exposures (including smoking and air pollution), the frequency of symptoms such as cough, phlegm, breathlessness, and for details of hospital visits, treatments received, healthcare costs and impact on their lifestyle. Standardised questionnaires (provided by IMPLALA), aimed at delineating the severity of, and risk factors for lung disease, will be validated for use in other post-TB populations. Participants’ answers will be linked to data already gained from the LAT study (after consent has been given).

**3 monthly phone calls or follow up**

Study staff will make contact with participants via a phone call every 3 months (or if unable to the reach them on phone, they may follow up them at clinic or in their home), with the aim of reducing lost to follow up, and also recording healthcare seeking behaviours that have occurred in the last 3 months.
A.5  **PARTICIPANTS:** Please state the number of research participants to be recruited. If you are unable to give precise figures, please give estimates.

<table>
<thead>
<tr>
<th>AGE/SEX</th>
<th>Neonates (&lt;28 days)</th>
<th>Infants (1-12 months)</th>
<th>Young children (1-4 years)</th>
<th>Older children (5-9 years)</th>
<th>Pre-adolescents (10-14 years)</th>
<th>Adolescents (15 years – &lt; age of majority)</th>
<th>Adults (≥ age of majority)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td>160</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td>160</td>
</tr>
</tbody>
</table>

A.5.2  **ELIGIBILITY CRITERIA**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Reason for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Adults (over the age of 15) who have been referred from the LAT study to the post-PTB chest clinics in Queen Elizabeth Hospital.</td>
<td>Exclusion criteria:</td>
<td>1) The pattern of TB differs in children to adults</td>
</tr>
<tr>
<td>2) Adults must have given informed consent</td>
<td>1) Under the age of 15 2) Unable to give fully informed consent</td>
<td>2) Informed consent is required for the study</td>
</tr>
</tbody>
</table>

A.5.3  **SAMPLE SIZE:** Please justify your choice of sample size (as described in A.5.1). Please ensure that the sample size calculation is based on the primary outcome measure as detailed in A.3.

Most sample size calculations will be performed on a computer and we encourage applicants to include screen shots of these calculations. Note that screen shots are not sufficient in themselves and need to be accompanied by justification of the values used in the calculations.

We will recruit 400 adults (over the age of 15 years). If we recruit 160 participants, either with or without post TB lung disease (320 in total), who are followed up every six months after baseline for three visits, we will be able to detect with at least 80% power an annual rate of decay in lung function of no less than 17.83 ml/year. This allows a total lost to follow up rate of 20% from the 400 participants. These power calculations have been reviewed and agreed by the biostatistics departments at Lancaster Medical School. Healthcare seeking behaviours will be collected for secondary data analysis.

A.5.4  **VULNERABLE GROUPS:** Please identify vulnerable groups that will be included in this study. Also state how you will minimise any harm to each group identified.
1) Participants are potentially from a poor background and have chronic disease. We will ensure that they are fully reimbursed for their time and travel. We will also ensure a local worker fully explains the study to them in their local language.

2) Adolescents under the age of 18. The study team will not enrol them unless they are confident their parent or guardian and the adolescent fully understand the study. This will be done in the local language. A number of the original LAT study may still be between the ages of 15 and 18. We wish to represent the entire age range of the original study, and therefore will offer the opportunity of taking part to adolescents and adults alike.

### A.5.5 RECRUITMENT PROCESS

Please detail the procedures for how you will be approaching each group of study participants. Where will recruitment take place? Who will be responsible for recruitment of participants? How much time will participants have to decide to take part?

Participants will be recruited from referrals to the respiratory clinic at Queen Elizabeth Hospital, Blantyre. This is run by local physician Doctor Peter Banda. The research nurse will screen the participants and recruit according to the inclusion and exclusion criteria. Participants will be given written and verbal information in their own language. The objectives, possible risk and details of the study are in the patient information sheet and will also be given verbally. Participants will be given up to a month to decide, but maybe recruited at the time if they would prefer not to travel again. Participants will have a contact number of the study nurse and field workers so that recruitment can be discussed at time suitable to them.
### A.6 MAJOR METHODS OF ANALYSIS: What are the major methods you intend to use to analyse the data?

These should be clearly linked to the outcome measures listed in section A.3

Questionnaire and longitudinal lung function data will be analysed using odds ratios, Risk Ratios and regression models. The relationship of post-TB lung disease with acute health access will be explored using longitudinal mixed effect models. Lung function change overtime with be the major outcome of objective one. Key variables including age, sex, smoking status and clinical severity measured by oxygen levels, respiratory, previous radiological phenotyping, 6 minute walk test will be included in the model.

Acute access to health care will be measured as an outcome, included in the main model will be clinical severity measured by oxygen levels, respiratory, previous radiological phenotyping, 6 minute walk test and spirometry.

For the purposes of the conceptual model, the exposed group will be those with evidence of post-TB lung disease and the unexposed group will be those without evidence of post-TB lung disease as defined by the previous LAT based on radiological results and clinical data.

### A.7 QUALITY ASSURANCE: What procedures are in place to ensure the quality of the data? Consider:

i. data collection and processing
ii. data analysis
iii. data storage

#### Data collection and Processing

Each study procedure will have a standard operating procedure (SOP) to aid study staff in achieving a quality output and reduce variability of results.  
All study equipment will be calibrated and maintained according to manufacturer’s instructions.

Before the study commences, study staff will receive full training relating to:
- Enrolment of participants – including eligibility criteria
- Obtaining informed consent
- Completion of electronic CRF
- Study SOPs
- Performing spirometry tests
- Performing clinical test oxygen saturation, respiratory rate and 6 minute walk test.

Spirometry traces will be reviewed by two assessors for adherence to within-manoeuvre and between-manoeuvre quality criteria.

Study field workers will be supervised by senior team members, to ensure SOPs are adhered to, and to identify any additional training needs.

#### Data Analysis

Analysis will be done as per A6. Results will be presented in tabulated format, giving mean or median values and 95% confidence intervals. Comparison will be made between those with post-TB lung disease and those without. Relationships between healthcare usage and chronic lung disease will be explored using tables and where required graphs and / or pictorial representation.

#### Data storage

Each participant included in the trial will have their own electronic case report form (CRF) that will be identify by the participants ID number and date of birth. An electronic CRF will be used to make the large number of CRFs manageable and provide real-time data entry, internal validity and consistency checks. All electronic devices used will be password-protected and encrypted to industry standards. CRFs will be treated as confidential documents and held and backed up on a secure server.
### SECTION B
**PROCEDURES AND PATIENT CARE**

#### B.1 PROCEDURES
Please detail any clinical, non-clinical or other research procedures to which participants will be subjected.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>To be carried out by:</th>
<th>Who is the person employed by?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Spirometry</td>
<td>Research nurse or trained field worker</td>
<td>MLW</td>
</tr>
<tr>
<td>2. 6 minute walk test</td>
<td>Trained field worker</td>
<td>MLW</td>
</tr>
<tr>
<td>3. Questionnaires</td>
<td>Trained field worker</td>
<td>MLW</td>
</tr>
<tr>
<td>4.</td>
<td></td>
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<tr>
<td><strong>Continue if necessary</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### B.2 TRAINING
Please indicate the basis on which the persons identified in B.1 are thought to be competent to carry out these procedures. List any training of staff which will be required prior to commencement of the study.

According to ICH GCP ([International Conference on Harmonisation - Good Clinical Practice](https://www.ich.org/)), all research staff should have a minimum of Protocol and GCP training, and training on Consent where appropriate. These mandatory training requirements should be in place at the time the study commences.

<table>
<thead>
<tr>
<th>Staff Member</th>
<th>Title</th>
<th>Experience/competencies</th>
<th>Training Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malumbo N’goma</td>
<td>Field worker</td>
<td>Worked on previous LAT study. Has had spirometry training via PATS. Has GCP.</td>
<td>Protocol training. Updated GCP when runs out.</td>
</tr>
<tr>
<td>Hygiene Kumwenda</td>
<td>Field worker</td>
<td>Worked on previous LAT study. Has questionnaire and GCP training.</td>
<td>Protocol training. Updated GCP when runs out.</td>
</tr>
<tr>
<td>Bright Mnesa</td>
<td>Field worker/Data officer</td>
<td>Worked on Child lung health study. Trained in children and adult spirometry by PATS. Experience of managing child lung health data at MLW. GCP trained</td>
<td>Local training on the new LAT2 questionnaire and data management. Update GCP when run out and protocol training.</td>
</tr>
</tbody>
</table>
Emma Nyirenda
Filed worker
Worked child lung health. Trained in children and adult spirometry by PATS. GCP trained.
Protocol training. Updated GCP when runs out.

B.3 STANDARD PATIENT CARE: Please explain if the procedures outlined in B.1 are part of the normal clinical work of the staff who will perform the procedure.

If this is not a clinical study, check box and go to B.4  
No, it is not part of their normal clinical work but they are only employed as research staff and none of procedures are new to them.

B.4 END OF STUDY TREATMENT: For intervention studies, what steps will be taken to make successful interventions or treatment available to all participants at the end of the study?

If this is not an intervention study, check box and go to Section C  

SECTION C
ETHICAL ISSUES AND CONSEQUENCES
Consider how you will protect the health, dignity and well-being of participants, staff and members of the public. Please also show awareness of impact on health services, and whether there are any further ethical issues.

C.1 ADVERSE EFFECTS, DISCOMFORT OR RISKS: Outline the potential adverse effects, discomfort or risks that may result from the study for participants, investigators and members of the public and how you will minimise them.

C.1.1 Participants
Potential adverse effects, discomfort or risks

1) The participant is using their time to take part in the study, this could be used for work.
2) Spirometry effort/discomfort

Steps to be taken to minimise adverse effects, discomfort and risks

1) The participant will be given 10USD (set by COMREC) for their participation. This will cover time lost due to work and travel.
2) The patient will be screened as per the SOP for any contraindications to spirometry. They will also only repeat it a maximum of 8 times pre and post to reduce fatigue. Spirometry is a recognised clinical measure that carried minimal risk. To reduce infection risk a new spirette will be used for every participant. Spirometry will be carried out by trained staff.

C.1.2 Investigators
Potential adverse effects, discomfort or risks

1) Risk of infection if participant does have active TB
2) Transport risk on home visit

Steps to be taken to minimise adverse effects, discomfort and risks

1) The risk is low as the focus is on those already treated. However participants are asked about TB as part of the questionnaire
and staff can refer to the respiratory clinic. All staff also have adequate PPE and infection control training.
2) Staff will use MLW transport or recognised local means. They have PPE as required.

<table>
<thead>
<tr>
<th>C.1.3 Members of the public</th>
<th>Potential adverse effects, discomfort or risks</th>
<th>Steps to be taken to minimise adverse effects, discomfort and risks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**C.2 CONSEQUENCES FOR LOCAL HEALTH SERVICES**

What demands will this research place on local health services?
The demand will be minimal. The participants will be recruited from referrals from the respiratory clinic. Unwell participants will be referred to the normal respiratory clinic for assessment.

Detail how the design of the research project takes these demands into account
The research nurse will do the majority of the recruiting, it will therefore not fall to the respiratory clinic staff. We have worked with Dr Peter Banda and he believes the clinic has capacity to receive unwell participants from the study as it is likely they would have presented anyway. Dr Jamie Rylance will also oversee this and work in partnership with Dr Banda to maximise cross-learning and peer-supported clinical practice.

**C.3 ADDITIONAL ETHICAL ISSUES**

Outline any other ethical issues which are not described above.
None.

Please indicate how you plan to deal with these ethical issues
N/A

**SECTION D**
MONITORING AND OVERSIGHT

D.1 **MONITORING AND OVERSIGHT:** Please give details of the proposed arrangements for independent monitoring and oversight of the trial and how any data and safety monitoring function will be carried out.

If this is not a clinical trial, check box and go to D.2

D.2 **RECORDING AND REPORTING SAEs:** Provide details of how you propose to manage the recording and reporting of serious adverse events.

If this is not a clinical trial, check box and go to Section E

**SECTION E**
PRIVACY, INFORMED CONSENT AND ASSENT

E.1 **INFORMED CONSENT** (please pay particular attention to the guidance notes for this section)
### E.1.1 Obtaining Informed Consent

Please give details of how you will obtain informed consent / assent / proxy consent. You must include details of:

1. Information given to participants
2. Who will deliver the information
3. Consideration of local circumstances and
4. How consent will be recorded.

Multiple consent / assent groups should be clearly defined.

The participant will be given a written information sheet, using the University of Malawi College of Medicine template, to read in English or Chichewa. This will be read out to all participants to facilitate discussion and ensure that inability to read is not an obstacle to participation. It will be read either in English or the local language (Chichewa) at the choice of the individual participant. The study team are fluent in both languages. Consent will be obtained by either the research nurse or trained field workers.

Written informed consent will be obtained from all participants. A mark witnessed by someone independent to the study will be accepted where participants are unable to sign. The consent form will be read out aloud to all who are unable to read. It can be read out in either English or Chichewa. Those under the age of 18 but over the 15 will require a signature from their legal parent or guardian. If the parent or guardian can’t sign, a mark witnessed by someone independent to the study will be accepted. The adolescents will must also assent to participate, the field team will ensure both parents and the adolescent are in agreement to participate.

Consent will be recorded on individual consent forms (attached as part of this application) and will stored in locked filing cabinet according to MLW’s data protection policy.

### E.1.2 Constraints

<table>
<thead>
<tr>
<th>Constraint to obtaining consent</th>
<th>Mitigation of constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant unable to read</td>
<td>Form and consent form will be read out in the language the participant speaks.</td>
</tr>
<tr>
<td>Participant unable to sign</td>
<td>A mark can be made (such as thumb print) in the presence of an independent witness.</td>
</tr>
</tbody>
</table>

### E.2 Compensation

Participants will be given 10USD per visit to reimburse for travel and provide compensation of their time. This is set by COMREC.

### E.3 Privacy and Confidentiality

For each type of data to be collected, please describe how participant privacy and confidentiality will be maintained during data collection, analysis and storage. Will a Trial Master File be used and where will it be kept?

1. Spirometry data will be anonymised with only the participants initials, ID and date of birth being recorded. It will be stored on the NDD (spirometer manufacturer) database that is standard with spirometer and backed up on a central server or/and password protected laptop.
2. 6 minute walk tests and clinical data will be recorded as part of the electronic patient record. They will be anonymised with only ID, initials and date of birth being recorded.
3. Questionnaires will be collected on password protected tablets and will be anonymised containing ID numbers and participant initials only. A master file will be kept in accordance with MLW policy. It will be kept in the research team office, in a locked filing cabinet.

### E.4 Dissemination

Please outline what plans you have for dissemination of results.
The trial findings will be presented at international conferences (such as the International Union against Tuberculosis and Lung Disease) and published in peer-reviewed journals with open access. We will present our findings at the College of Medicine research dissemination conference (via COMREC). We will communicate the findings of our work to participants using the MLW community engagement team. We will present our work through other community engagement activities held by the College of Medicine, MLW and LSTM in Malawi and the UK.

A copy of the final report, published papers and conference abstracts will be submitted to:
- College of Medicine Research and Ethics Committee
- College of Medicine Library
- Health Sciences Research Committee
- University Research and Publication Committee

Check List:
The following Check List must be completed. Please confirm that the following are enclosed.

<table>
<thead>
<tr>
<th>Please do not staple any of the below.</th>
<th>Enclosed</th>
<th>Not Applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Completed Internal School Transfer Form (ISF) for administration charges</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>6 Copies of the completed Application Form</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>2 Copies of the Research Protocol (N.B. version control)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>6 Copies of the Questionnaire/case record form</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>6 Copies of the Consent Form (N.B. version control)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>6 Copies of the Participant Information Sheet (N.B. version control)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>6 Copies of the Translator Agreement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Copies of the Draft interview/FGD or observation/Check list enclosed (if used)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>6 Copies of the Declaration page - last page of application (1 signed and initialled by the applicant plus 5 copies)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Collated Applications – please ensure you collate all documents into 6 separate applications and NOT 6 copies of each document</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The collated paper applications should be sent to: Lindsay Troughton, Secretary, Research Ethics Committee, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA Plus one combined pdf application via e-mail: lstmrec@lstmed.ac.uk

If proposal is for work relating to a MPhil/PhD:

<table>
<thead>
<tr>
<th>Supervisor / Tutor</th>
<th>Dr Jamie Rylance, Dr Kevin Mortimer, Prof Bertie Squire,</th>
</tr>
</thead>
<tbody>
<tr>
<td>Department</td>
<td>Clinical Sciences (lung health)</td>
</tr>
</tbody>
</table>

By signing below, I confirm that:
- The application is clearly written and can be understood by a lay person
- The objectives can be met by the proposed methodology
- Participants will be identified, recruited and consented in accordance with ethical guidelines
- The participant information sheets and consent / assent forms are appropriate for the target audience

| Supervisor / Tutor Signature |        |
DECLARATION: TO BE SIGNED BY MAIN APPLICANT

Applicants must initial each declaration or tick N/A in the right-hand column if applicable

<table>
<thead>
<tr>
<th></th>
<th>Initial (by hand)</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>I confirm that the details of this proposal are a true representation of the research to be undertaken.</td>
<td></td>
</tr>
<tr>
<td>ii</td>
<td>I will ensure that the research does not deviate from the protocol described.</td>
<td></td>
</tr>
<tr>
<td>iii</td>
<td>I confirm that I and all staff who are involved in the research and/or in obtaining consent from participants will receive formal training in GCP and the requirements of the Human Tissue Act 2004 before the research project commences.</td>
<td></td>
</tr>
<tr>
<td>iv</td>
<td>If significant protocol amendments are required as the research progresses, I will submit these to the Liverpool School of Tropical Medicine Research Ethics Committee for approval.</td>
<td></td>
</tr>
<tr>
<td>v</td>
<td>Where an appropriate mechanism exists, I undertake to seek additional in-country Ethical Approval in the country(ies) where the research is to be carried out and abide by local regulations, including those on data and human tissue.</td>
<td></td>
</tr>
<tr>
<td>vi</td>
<td>I agree to abide by the ethical principles underlying the Declaration of Helsinki and all relevant LSTM Standard Operating Procedures (SOP) relating to research conduct (available on LSTM Clinical Trials Support Package or by contacting the Research Governance &amp; Ethics Office).</td>
<td></td>
</tr>
<tr>
<td>vii</td>
<td>I understand that all conditions apply to any co-applicants, researchers and other staff involved in the study, and that it is my responsibility to ensure that they abide by them.</td>
<td></td>
</tr>
</tbody>
</table>

Where application form has been completed by junior researcher on behalf of the PI

viii) I have reviewed this application and am satisfied that it is at an acceptable standard

ix) I will provide the Research Ethics Committee with an annual report, due each year on the original approval date, and an end of study report once all activities are completed.

For studies using 'human tissue'*
x) I confirm I will abide by LSTM’s Policies and Standard Operating Procedures relating to activities involving human tissue

*Human tissue (relevant material) is defined as any material that has come from a human body and consists of, or includes, human cells. Further detail can be found at [http://www.hta.gov.ac.uk/legislationpoliciesandcodesofpractice/definitionofrelevantmaterial.cfm](http://www.hta.gov.ac.uk/legislationpoliciesandcodesofpractice/definitionofrelevantmaterial.cfm)

Signed: [ ] Date: [ ]

From time to time the Committee uses past ethics applications for training purposes or to give examples to new applicants. In all cases the applications are anonymised.
If you DO NOT consent to your application being used for these purposes, please tick the box. [ ]
PARTICIPANT INFORMATION SHEET

LAT 2 STUDY
Life after Tuberculosis

My name is............ and I work for the Malawi-Liverpool-Wellcome research institute. You are being invited to participate in a research study that we are running. Your participation is voluntary. This means you can choose to participate if you want to. If you do not wish to participate, nothing bad will happen – you will continue to receive the care and treatment you need at the hospital or health centre as usual. I would like to tell you some information about the study. Please ask questions if there is anything you do not understand.

What is the name of the study?
The name of the study is ‘Life after Tuberculosis (LAT2)’.

Who is in charge of this study?
This study is being led by a researcher (Rebecca Nightingale) at the Malawi-Liverpool-Wellcome research institute. Her contact details are listed at the end of this information sheet.

Why are we doing this study?
We are doing this study to learn about the lung damage that TB infection leaves behind after treatment, and how this affects people. As part of the study we will use questionnaires that have been written for this purpose, if they work well the questionnaires can be used in African counties.

Tuberculosis is an infection that can damage the lungs, making people feel very unwell. The tablets you took can cure the infection and making you feel better, but some people are left with scarring of the lungs even after treatment. This is similar to the way in which you can be left with a scar on the skin after you have cut yourself, after the skin has healed.
We would like to find out if this scarring of the lung causes people in Malawi any problems - such as breathlessness, cough, or chest infections - after they have finished their TB treatment and are cured of the infection. We would like to know how these problems affect their lives and their work.

We hope that this will help us to provide better health care and support for people in Malawi who have lung scarring in the future.

**How was I chosen?**

We are asking you to join this study because you have recently been referred to the post TB chest clinic at Queen Elizabeth Central Hospital (QECH), Blantyre and have been treated for TB in the last 2 years. We are hoping to include a total of 300-400 people like you, from Blantyre, who have referred to this clinic.

**What does this study involve?**

This study will last 18 months in total. During this time we will see you a minimum of 3 times approximately every 6 months to complete some questionnaires and tests. We shall also contact you each 3 months to monitor your progress. At each visit we would like to complete some tests and questionnaires at QECH. If you are unable to come to QECH we may be able to visit you at your home.

We would also like you to go to your local health centre or come to the hospital if your breathing gets suddenly worse during the year, for example if you have a chest infection. You can inform the research team if this happens.

We would like to look at your Health Passport to learn more about your health. We would also like to look at the information about your TB treatment in the National TB Register. If you were involved in the LAT study we would like to access your previous results so that we can compare them to now.

**What are the questionnaires about**

We will ask you to fill in some questionnaires at each of the study visits. The study team will ask you the questions. In these questionnaires we will ask you about your breathing and your general health before, during, and after your TB treatment. We will ask you about how your health problems affect your daily life, and your ability to work and earn money. We will also ask about you, about possible things that might effect your lungs such as smoking, cooking and the type of job you do.

You will not have to answer any questions if you do not want to, and you can stop the interviews at any time.

All of the questionnaires will take approximately 1.5 hour to complete.
What tests are included in the study?

The tests in this study will tell us if you have any scarring of your lungs, and will show us how well your lungs are working. They will also tell us about your general health.

They will include:

1. **Breathing tests**
   We will help you to do at each 6 monthly visit. This test involves taking a deep breath in, and then blowing out into a small machine. We will measure how big your lungs are, and how well they are working. The test takes 30 minutes to complete.

2. **Walking tests**
   You will be asked to do a walking test once a year. In this test we will measure how far you can walk, on flat ground, in 6 minutes. You will be able to walk at a speed that is comfortable for you, and you can stop if you feel tired or cannot continue.

If you are sick we may refer you for some tests to check that you have not caught TB again. These will be done at QECH.

You will not have to do any tests if you do not want to, and you can stop the tests at any time.

Is there any harm to me from doing this study?

No – we do not believe that there will be any long-term harm to you if you participate in the study.

The breathing and walking tests may make you feel dizzy, tired, or breathless for a short time – these feelings will go away if you sit down and rest.

Are there any benefits to me from doing this study?

The tests that you will receive as part of this study will give us a lot of information about your lungs. We will give you the results of these tests for you to share with any other healthcare providers that you see. We hope these test results will help them to better treat any lung problems you have. We will pay you for your time and transport.

What will happen if you find anything wrong with my lungs or health during the study?
If we find anything wrong with your lungs on your tests, we will invite you to come and see a lung doctor at Queen Elizabeth Central Hospital. Sometimes these abnormal findings get better by themselves, but the doctor will be able to advise you on any other tests or treatment that you need. We will pay for the costs of your transport to QECH for this appointment.

If you do need any treatments, we will refer you to the correct team at Queen Elizabeth Central Hospital, who will help you to get the treatment that you need.

**Who will pay for my tests and travel costs?**

We will pay for all of the tests in the study.

We will reimburse you for your time and travel to the equivalent of 10 USD in Malawian Kwacha.

We will **not** be able to reimburse you for other costs of your normal TB treatment or any other non-TB health problems that you report during this study.

**Will anyone else find out about what I have said, or what my test results are?**

All of the answers that you give to our questions will be confidential. Your answers will be stored on a secure central computer system, and only the research team will be able to see them. The phones and tablets used to collect your answers will be kept in a locked room, and only research staff will be able to use them. Your test results will also be confidential. Only the research team will be able to see these results.

We will remove your personal information from the computer system as soon as possible, so that you will be identified by a number only in our records. All of the records will be stored in a secure and confidential way.

If you are unwell we will refer to the correct clinic at Queen Elizabeth Central Hospital, Blantyre or local health centre.

**What will happen if I do not participate in this study?**

Your participation in the study is voluntary – it is your choice. If you choose not to do this study, nothing bad will happen to you. You will continue to receive the care and treatment you need at the hospital or health centre as usual.

**What will happen if I withdraw from the study?**

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You can withdraw from all or part of the study at any time – it is your choice. Nothing bad will happen to you if you decide to withdraw. You will continue to receive the care and treatment you need at the hospital or health centre as usual.

**What will you do with the results of the study?**

The main aim of the study is to make the care of people like you in Malawi better. We will use the results of this study to tell us how to help people who are left with lung scarring after TB treatment. Secondly we aim to use the questionnaires in other environments.

We may share what we learn with other people who are working to improve the health of patients who have had TB through lectures and publications, but your personal information will not be shared.

**Can I find out the results of the study?**

Yes – we would really like to share the result of the study with you. We will be holding vents in conjunction with MLW’s communications team, once we have finished the study, and we would be very happy if you would come to these. You can also contact the research team directly for the results.

**Who can I speak to with questions about this study?**

We are happy to answer any questions that you have, now or later.

If you have any questions or concerns about this study, you can call
Rebecca Nightingale / Jamie Rylance / Beatrice Chinoko on 0998 319 219

**Who should I speak to if I have any complaints?**

If you would like to lodge any complaint regarding the study please contact:

COMREC Secretariat,
College of Medicine,
P/bag 360,
Blantyre 3.
Tel no. 019897666