Lung health across the life course in Malawi

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

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Contents

Lung health across the life course in Malawi: Dr. Sarah Rylance

Background: Chronic respiratory symptoms are common in Malawian adults and might be determined by lung development, growth and exposures in earlier life: alternative cooking methods, such as cleaner-burning cookstoves, have been proposed as a way to reduce biomass-fuel smoke exposure and improve lung health. Tailored strategies for resource-limited settings are needed to improve the management of common childhood respiratory conditions.

Aims: 1. To explore the prevalence of non-communicable lung disease and air pollution associated determinants in children and adults in rural Malawi 2. Evaluate a novel task shifting approach to asthma management for children.

Methods: Within the same rural Chikhwawa communities, we conducted a prospective cohort study of adults, collecting respiratory questionnaire data, spirometry and personal air pollution exposure measurements at three timepoints over 3-years, and a cross-sectional study, collecting similar data from children aged 6-8 years at one timepoint.

We also conducted a randomised-controlled trial and qualitative sub-study to evaluate the feasibility and effectiveness of a task shifting intervention, using non-medically trained asthma educators, on asthma outcomes. The intervention comprised detailed clinical assessment, optimisation of inhaled treatment, and asthma education delivered by lay educators. Asthma symptoms and exacerbations, spirometry and exhaled nitric oxide were assessed at 3-months.

Results: We recruited 1481 adults, mean (SD) age 43.8 (17.8) years, (654 with acceptable spirometry at ≥2 timepoints) and 804 children, mean (SD) age 7.1 (0.8) years, (522 with acceptable spirometry) in Chikhwawa. Forced expiratory volume in 1 second (FEV_1) and Forced Vital Capacity (FVC) decline were 30.9 ml/year (95% confidence interval (CI): 21.6-40.1) and 38.3ml/year (95% CI: 28.5-48.1), respectively: comparable to natural age-related decline seen in healthy non-smokers in high-income settings. Lung function z-scores, referencing Global Lung Initiative African-American predicted values, were similar in children and adults and we found no evidence of an association between personal air pollution exposure and lung function or respiratory symptoms. Secondary analysis of a sub-group of children from households previously enrolled in a cookstove trial suggested a potential benefit: children from intervention households had a lower carboxyhaemoglobin level and higher FVC z-scores compared to controls.

We recruited 120 asthmatic children at a tertiary hospital in urban Blantyre; 59 received the intervention, 61 continued with standard care in the outpatient clinic. At 3-months, we found a clinically and statistically significant improvement in the primary outcome: asthma control in intervention vs standard care group (increase in mean (SD) cACT score of 2.7 (2.8) vs 0.6 (2.8), $p<0.001$). In addition, fewer children receiving the intervention required emergency health care (7.3% vs 23.7%, $p=0.03$) or missed school (20.0% vs 61.0%, $p<0.001$) due to exacerbations. Children and carers described the positive impact of asthma education on their knowledge levels and increased confidence to self-manage symptoms.

Implications: Our findings from Chikhwawa suggest that lung function deficits seen in adults are present in childhood, and that early life influences are likely an important contributor to adult lung health. Future research should consider public health interventions addressing multiple adverse risk factors encountered *in utero* and early childhood.

Task shifting asthma education roles resulted in improved asthma outcomes and high levels of patient satisfaction, suggesting this could be an effective strategy in resource-limited settings. Further research is needed to assess the wider application of this approach across all levels of health facility.

Declaration

For the studies presented in chapters 3, 5 and 6, I was responsible for all research activities, including; study design, obtaining ethical approval in UK and Malawi, preparation of all study documents including electronic questionnaires, training and supervision of study teams, spirometry overreading, data cleaning and analysis, and manuscript preparation (as first author). Study approvals and documentation are included in the Appendices.

The focus group discussions and interviews in chapter 6 were facilitated in Chichewa and transcribed and translated into English by Lovemore Nkhalamba. Felix Limbani provided senior guidance on the qualitative study design, and Lovemore, Felix and I worked together to develop the thematic analysis and interpret the findings.

I began working on the Adult Lung Health Study (ALHS) (Chapter 4) during my MRes studies in 2017; I supervised the final year of data collection and study close-out, cleaned and analysed the data, including extraction and analysis of all the Aprovecho data and was first author for the resulting publication.

Spirometry overreading for ALHS was performed by Prof. Peter Burney and the BOLD centre (Imperial College, UK) for the baseline data, and by Lindsay Zurba (Spirometry Training Services Africa, South Africa) for the follow-up data.

All statistical analysis in this thesis has been performed by myself, with senior guidance from Dr. Chris Jewell (Lancaster University).

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This thesis is dedicated to my family, with special thanks

To Jamie, for your enduring belief that everything will work out alright in the end, and everything you do to make sure that you're right

To Arthur and Arwen, for inspiring me, encouraging me and helping to keep it all in perspective

To Mum and Dad, for your endless love and support

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I am grateful to Prof. Stephen Gordon and many friends and colleagues at Malawi-Liverpool-Wellcome (MLW) Trust, for providing a supportive and stimulating research environment. I first started thinking about the challenges of chronic disease care in 2010, as the consultant running the Paediatric general clinic at Queen Elizabeth Central Hospital in Blantyre: I am so fortunate to have been able to return to Malawi to conduct my PhD research and attempt to address some of my questions. It took me a while to get there but "Kuthamanga sikufika" – *Translation: One does not reach by rushing*

The Chikhwawa studies (Chapters 3 and 4) would not have been possible without the study participants, village leaders and community

representatives, the study team in Chikhwawa, MLW and Liverpool School of Tropical Medicine (LSTM), the CAPS trial steering committee and data monitoring committee, the Malawi Ministry of Health, and the African Clean Energy company.

The studies in Chapters 5 and 6 would not have been possible without the study participants and their families, and the hard-working study team; Beatrice Chinoko, Bright Mnesa, Emma Nyirenda, Malumbo Ng'oma and Hygiene Kumwenda. I am also grateful to Lovemore Nkhalamba and Felix Limbani for their invaluable assistance with the qualitative work in Chapter 6.

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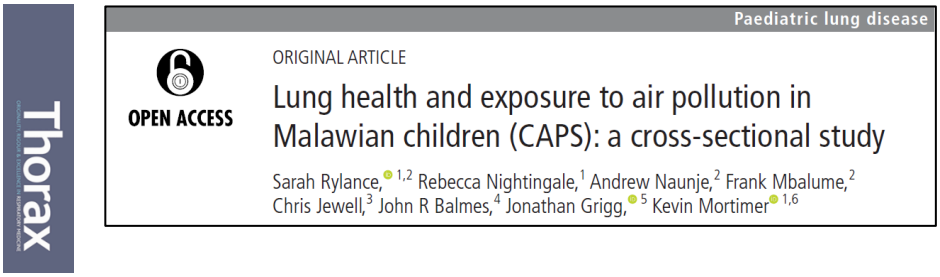
Publications and Awards

Publications arising from work within thesis

See appendices



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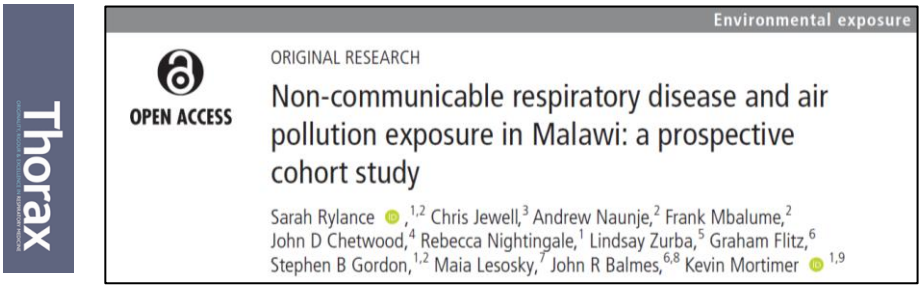

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Publications submitted or in preparation from work in thesis

Rylance S, Masekela R, Banda NPK, et al. Determinants of lung health across the life course in sub-Saharan Africa. *Accepted: The International Journal of Tuberculosis and Lung Disease*

Rylance S, Chinoko B, Jewell C, et al. Task-shifting to improve asthma management in Malawi: a randomised controlled trial. *In preparation*

Rylance S, Nkhalamba L, Muula A, et al. Task-shifting to improve asthma education at a tertiary hospital in Malawi: a qualitative analysis. *In preparation.*

Conference abstracts

Rylance S, Nightingale R, Naunje A, et al. Non-communicable lung disease and exposure to household air pollution in rural Malawian children: a cross-sectional study [abstract]. *The International Journal of Tuberculosis and Lung Disease* 2018; **22**(11): S316.

Publications related to and arising during the course of the PhD

Rylance S, Rylance J, McHugh G, et al. Effect of antiretroviral therapy on longitudinal lung function trends in older children and adolescents with HIV-infection. *PLoS One* 2019; **14**(3): e0213556.

Nightingale R, Lesosky M, Flitz G, Rylance SJ, et al. Noncommunicable Respiratory Disease and Air Pollution Exposure in Malawi (CAPS). A Cross-Sectional Study. *Am J Respir Crit Care Med* 2019; **199**(5): 613-21.

Simms V, Rylance S, Bandason T, et al. CD4+ cell count recovery following initiation of HIV antiretroviral therapy in older childhood and adolescence. *AIDS* 2018; **32**(14): 1977-82.

Rylance S, Mortimer K. Galloping Hooves in Africa: Horse, Zebra, or Wildebeest? *Ann Am Thorac Soc* 2017; **14**(5): 624-5.

Awards

Best oral presentation (PhD student): 23rd Research Dissemination Conference, College of Medicine, University of Malawi: November 2019.

List of tables

List of figures

List of abbreviations

ACT	Asthma Control Test
ALHS	Adult Lung Health Study
ART	Anti-Retroviral Treatment
ATS	American Thoracic Society
BMI	Body Mass Index
BOLD	Burden of Obstructive Lung Disease
cACT	Childhood Asthma Control Test
CAPS	Cooking and Pneumonia Study
CI	Confidence Interval
CLHS	Child Lung Health Study
CO	Carbon Monoxide
COHb	Carboxyhaemoglobin
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airways Pressure
DCHS	Drakenstein Child Health Study
EIB	Exercise Induced Bronchoconstriction
ERS	European Respiratory Society
ETS	Environmental Tobacco Smoke
FeNO	Fractionally exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 second
FGD	Focus Group Discussion
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
GLI	Global Lung Initiative
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HIC	High Income Country
HSA	Health Surveillance Assistant
ICS	Inhaled corticosteroid
ISAAC	International Study of Asthma and Allergies in Children
IQR	Interquartile range
IUGR	Intrauterine Growth Restriction
LBW	Low Birth Weight
LIC	Low Income Country
LLN	Lower Limit of Normal
LRTI	Lower Respiratory Tract Infection
LSTM	Liverpool School of Tropical Medicine
MDI	Metered Dose Inhaler
MIC	Middle Income Country
MLW	Malawi-Liverpool-Wellcome Trust Clinical Research Programme
MUAC	Mid Upper Arm Circumference
NCD	Non-communicable disease
NCD-L	Non-communicable lung disease
NHANES	National Health and Nutrition Examination Survey
NO_2	Nitrogen dioxide
OR	Odds Ratio
PEF	Peak Expiratory Flow

PM	Particulate Matter
$PM_{2.5}$	Particulate Matter ≤2.5µm
PM_{10}	Particulate Matter ≤10µm
PUFA	Polyunsaturated Fatty Acids
QECH	Queen Elizabeth Central Hospital
RCT	Randomised Controlled Trial
RR	Relative Risk
RSV	Respiratory Syncytial Virus
SABA	Short Acting $Beta_2$ Agonist
SAM	Severe Acute Malnutrition
SD	Standard Deviation
SDG	Sustainable Development Goal
SE	Standard Error
SO_2	Sulphur dioxide
sSA	Sub-Saharan Africa
TB	Tuberculosis
WHO	World Health Organization

1 General introduction

This thesis explores "Lung health across the life-course in Malawi", including novel research relating to non-communicable lung disease in Malawian children and adults. This chapter provides broad context for those which follow, introducing 1. the subject of non-communicable diseases (NCDs), in sub-Saharan Africa and Malawi more specifically, 2. the rationale for taking a life-course approach to lung health, and 3. the challenges of managing NCDs in a resource-poor setting.

1.1 Non-communicable diseases: an emerging global problem

NCDs present an increasing challenge for health care systems as the global burden of infectious diseases falls, due to improvements in disease prevention and treatment.[1] The most prevalent NCDs include cardiovascular diseases, cancers, chronic respiratory diseases and diabetes: conditions which require long-term management to minimise symptoms, improve quality of life and reduce risk of future adverse events.[2]

The World Health Organization (WHO) has identified the prevention and management of NCDs as a priority, emphasizing the importance of a life-course approach, with multi-stakeholder engagement and empowerment of people and communities.[3] The majority (approximately 80%) of global deaths from NCDs occur in low- and middle-income countries (LMICs).[3] Poverty and NCDs are intertwined; health systems in low-income countries are ill-equipped to detect and manage chronic conditions, and there are high household costs associated with long-term treatment. The 2030 Agenda for Sustainable Development recognises NCDs as a major threat and includes a target (Sustainable Development Goal 3.4) of reducing premature deaths from NCDs by one-third by 2030.[4]

Sub-Saharan Africa (sSA) is home to approximately one-third of the world's poorest population.[5] Historically, health care and research priorities have

focused on maternal-child health and infectious diseases. However, shifting demographic and lifestyle trends in the region, and a greater awareness of NCD risk factors has prompted increasing recognition of the importance of the dual burden of infectious diseases and NCDs, and the interaction between them.[6]

Malawi is one of the poorest countries in the world: classified as a Low Income Country (LIC) by the World Bank, 70% of the population live on less than $1.90 per day and the life expectancy at birth is 63.7 years.[7] The economy is heavily dependent on agriculture, and is particularly vulnerable to climatic shocks, Cyclone Idai (in March 2019) being a recent and devastating example. Malawi suffers from a shortage of trained clinical staff with 2 physicians and 28 nurses per 100,000 population, well below the WHO "critical shortage" threshold of 2.5 health professionals (including doctors, nurses and midwives) per 1000 population.[8,9] Currently, there are three tertiary level referral hospitals (Blantyre, Lilongwe and Zomba), 27 secondary level district hospitals, and 460 primary health care centres.[10] Most patients with NCDs are managed in one of the tertiary care facilities, although there is growing interest in decentralising care, with management of common conditions at the primary health care level.[11]

In Malawi, NCDs are associated with considerable direct and indirect costs, causing catastrophic household spending and exacerbating poverty.[12] NCDs are estimated to account for 32% of all deaths, with 2% reported to be due to chronic respiratory diseases.[13] Risk factors for NCDs are common in Malawi, with high blood pressure, sedentary lifestyle and raised body-mass-index (BMI) increasingly prevalent, particularly in urban areas.[14,15] The National Health Research Agenda recognises the burden of NCDs as a significant public health problem, including cardiovascular disease, cancer, diabetes and chronic lung disorders, especially asthma, as priority research areas.[16]

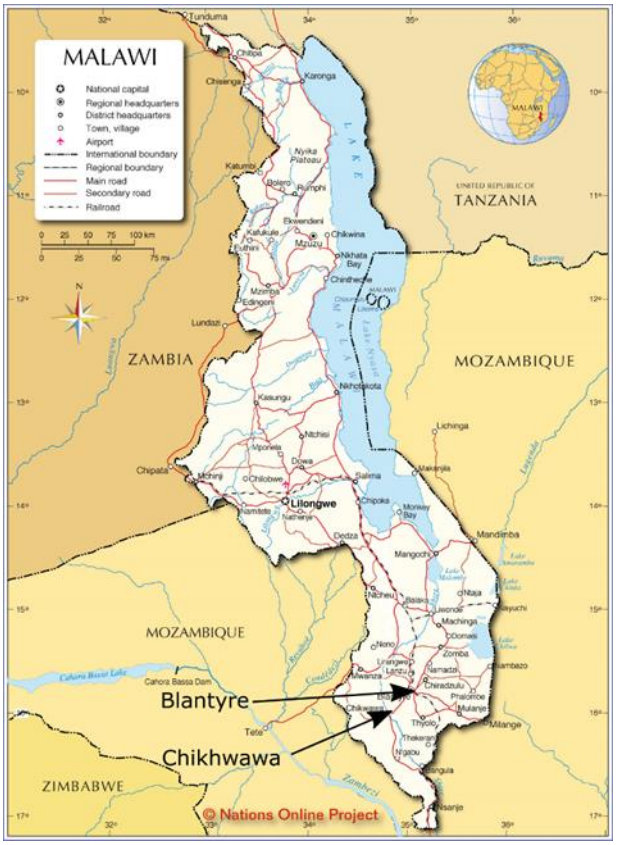

Figure 1-1. Map of Malawi, highlighting location of study sites: Blantyre and Chikhwawa

1.1.1 Non-communicable lung diseases

Non-communicable lung diseases (NCD-L) includes chronic obstructive pulmonary disease (COPD) and asthma; respiratory conditions associated with considerable morbidity and mortality. It is estimated that asthma affects 358 million people, and COPD 174 million people, worldwide.[17] The Global Burden of Disease Study 2016 reported COPD in the top ten causes of both death and disability worldwide.[2,18] Although a much rarer cause of death, asthma still accounts for 1000 deaths worldwide every day.[19] Asthma is a major cause of morbidity in childhood, ranking in the top ten causes of disability-adjusted life years in both younger and older children.[20]

There are limited data relating to NCD-L in sSA: the literature is reviewed in detail in Chapter 2.

Considering Malawi, there is no published research relating to NCD-L in children and the local prevalence of asthma is unknown. At Queen Elizabeth Central Hospital (QECH) both children and adults frequently attend the emergency department with acute wheeze, and severe cases are admitted to the wards. Adults with presumed COPD attend a weekly outpatient respiratory clinic, but limited access to spirometry prevents formal diagnosis.

Malawi is one of the few sSA sites involved in the Burden of Obstructive Lung Disease (BOLD) Initiative. BOLD was developed to explore the global prevalence and risk factors associated with COPD in adults with data, including pre- and post-bronchodilator spirometry, collected from 12 initial sites in 2006.[21] Data collected following this protocol in urban Blantyre (in 2013-2014), found chronic respiratory symptoms in 11.8% of adults, with low rates of spirometric obstruction (3.6%), and high rates of low Forced Vital Capacity (FVC) (38.6%), when compared to Caucasian spirometry reference ranges.[21,22]

In light of these results, a corresponding study was conducted in rural Chikhwawa (in 2014-2015) with similar findings; 13.6% of adults reported chronic respiratory symptoms, with spirometric obstruction in 8.7% and decreased FVC in 34.8%.[23] These findings raised concerns, as decreased FVC has been associated with increased mortality, prompting two further epidemiological studies which each form a chapter in this thesis; [24,25]

The **Child Lung Health Study (CLHS): Chapter 3**: is a cross-sectional study, investigating whether children show similar patterns of lung health to adults from the same communities.

The **Adult Lung Health Study (ALHS): Chapter 4**: is a longitudinal cohort study, following the adults included in the initial rural BOLD study, to explore whether the decreased FVC previously observed in Malawian adults is a result of accelerated lung function decline.

Both the CLHS and ALHS were conducted in Chikhwawa: this was also the site for the Cooking and Pneumonia Study (CAPS). CAPS was a community-level

cluster randomised controlled trial (RCT) to evaluate whether an intervention comprising two cleaner burning biomass-fuelled cookstoves and a solar charger would reduce the incidence of Integrated Management of Childhood Illness (IMCI)-defined pneumonia in children under the age of 5 years compared to continuation of traditional cooking methods.[26] CAPS recruited households from village clusters in Chikhwawa between December 2013 and February 2016. The primary intention-to-treat analysis found no difference in pneumonia incidence the between the two trial arms. The overlap of study participants in CAPS, CLHS and ALHS facilitated exploratory sub-analyses to assess the effect of the cookstove intervention on air pollution exposure, respiratory symptoms and lung function in children and adults from these communities.

1.2 The case for a life course approach to lung health

Under ideal circumstances, lung function increases steadily through childhood, with a steep climb during adolescence, reaching a plateau in early adulthood and then declining gradually as part of normal ageing.[27] Lung growth and development may be influenced by factors present across the life course, which may reduce growth or accelerate decline, as illustrated in Figure 1-2.

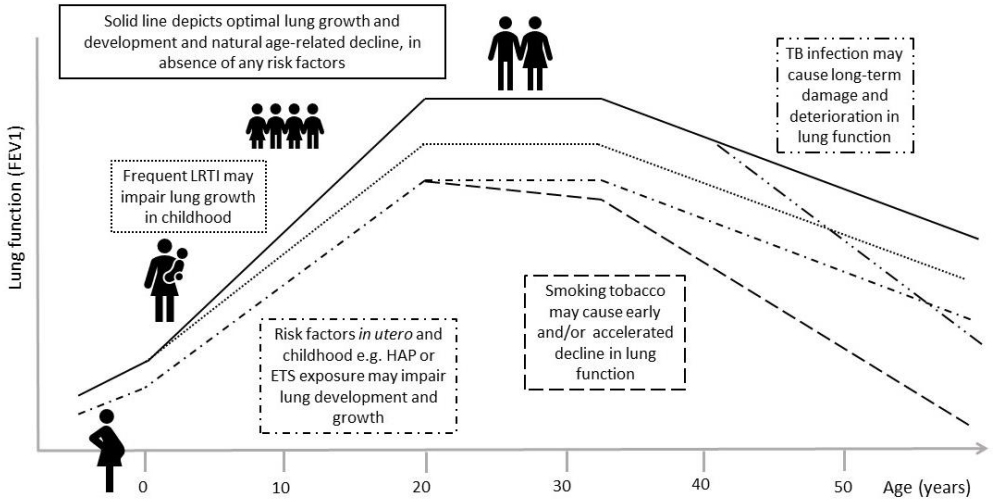

Figure 1-2. The impact of common risk factors encountered in sSA on lung function trajectories across the life course.

Trajectories shown (not to scale) demonstrate possible impact of adverse factors acting in childhood (dotted), *in utero* and childhood (dot-dash), in early adulthood (long dash) and later adulthood (long dash-dot-dot), compared to optimal lung growth (solid line).

ETS, environmental tobacco smoke; FEV1, Forced Expiratory Volume in 1s; HAP, household air pollution; LRTI, lower respiratory tract infection

Longitudinal cohort studies have established that lung function deficits detected in early childhood, persist through adolescence and into adulthood, even in the absence of respiratory symptoms.[28,29] Reaching adulthood without having achieved maximal lung function, is a risk factor for development of COPD, as age-related lung function decline starts from an already reduced level.[30] Furthermore, wheezing and impaired lung function in early childhood are associated with persistent wheeze, relapsing wheeze and new-onset asthma in young adults.[31,32]

Risk factors for asthma and COPD overlap; persistent asthma in childhood is a risk factor for obstructive lung disease in adulthood.[33,34,35] This overlap has prompted a call to redefine airways disease; to move away from age-related categories, and to consider airway disease in the context of a developmental trajectory across the life course, from birth (or even before birth) to old age.[36] Factors which might adversely affect lung development and growth *in-utero*, during the perinatal and neonatal period, childhood and into adulthood are

commonly encountered in low-income settings such as Malawi, including low-birth weight, prematurity, air pollution and respiratory infections.[37,38,39,40,41]

1.3 Non-communicable disease management in low-income countries

Health care systems in LIC have previously focused on the prevention and management of acute communicable diseases (such as malaria, gastroenteritis, and pneumonia) which accounted for high mortality rates, particularly in young children. Malawi has made great progress in tackling these diseases, meeting the Millennium Development Goal 4 target to reduce under-5 mortality by two-thirds between 1990 and 2015.[42] Acute infectious illnesses are usually managed during a single visit to a pharmacy or health centre, with a short course of medication (antibiotics or antimalarial treatment).

However, non-communicable respiratory diseases such as asthma and COPD are chronic conditions requiring treatment over many years to reduce symptoms and prevent exacerbations and associated morbidity. The need for long term medications and ongoing monitoring to manage chronic conditions, requires a paradigm shift in health care provision, with education of patients, health care providers and communities.

Non-communicable airways disease processes, and challenges to diagnosis and long-term treatment are common to adult and paediatric clinical practice. Under-resourced health services, with lack of appropriately trained clinical staff, diagnostic capability, and an unreliable supply of treatment, impact greatly on the quality of chronic disease management in LIC.[43] Patients and their families may lack the knowledge to understand their medical condition, and the importance of adherence to long-term medications. Financial barriers to accessing healthcare, and cultural beliefs and misconceptions may further contribute to poor compliance and inadequate disease control.

Sub optimal management of respiratory conditions in earlier life may have long-term detrimental effects on adult lung health. It is therefore important

to optimise the management of common childhood respiratory conditions, with consideration given to the constraints of resource-poor settings. The randomised controlled trial and qualitative sub-study described in chapters 5 and 6 evaluate a task shifting approach, appropriate for a LIC setting, to improve asthma outcomes in children.

1.4 Rationale for this thesis

This thesis will explore non-communicable airways diseases across the life course, in a low-income setting. The studies comprising this thesis have all been conducted in Malawi, in both urban (Blantyre) and rural (Chikhwawa) settings (Figure 1-1) and have relevance to other LIC, particularly in sSA.

1.4.1 Broad aims

1. To explore the prevalence of chronic respiratory symptoms and spirometric abnormalities, and air pollution associated determinants, in children and adults in rural Chikhwawa.
    - Do children show similar patterns of respiratory symptoms and lung function abnormalities as adults from the same communities?
    - Is decreased FVC previously reported in Malawian adults due to accelerated decline in lung function?
    - What is the impact of household air pollution on respiratory symptoms and lung function?
2. To evaluate a novel task shifting approach to asthma management for children.
    - What is the burden of asthma symptoms among children attending outpatient clinic in urban Blantyre?
    - Can a task shifting intervention improve asthma outcomes for children?
    - Is task shifting asthma education to non-clinical staff feasible and acceptable?

Specific objectives are listed within each chapter.

1.5 Outline of thesis

Chapter 2. Non-communicable lung disease in sub-Saharan Africa: a review of the literature

Chapter 3. Lung health and exposure to air pollution in Malawian children: a cross-sectional study (Child Lung Health Study: CLHS)

Chapter 4. Non-communicable respiratory disease and air pollution exposure in Malawi: a prospective cohort study (Adult Lung Health Study: ALHS)

Chapter 5. Task-shifting to improve asthma management in Malawi: a randomised controlled trial

Chapter 6. Task-shifting to improve asthma education at a tertiary hospital in Malawi: a qualitative analysis

Chapter 7. Summary of findings and implications

2 Non-communicable lung disease in sub-Saharan Africa: a review of the literature

This chapter is a review of the literature on non-communicable lung disease (NCD-L) in sub-Saharan Africa (sSA). It is deliberately broad as it aims to provide a wide perspective on our current state of knowledge about NCD-L in low- and middle-income countries (LMIC) in sSA, to put the original research that comprises the body of this thesis in context.

The epidemiological studies in chapters 3 and 4 describe NCD-L in rural Malawi and explore factors which might influence lung health, in both children and adults. The first half of this review will discuss the definitions of NCD-L, NCD-L epidemiology among children and adults in sSA, and factors which influence lung growth and development across the life course.

2.1 Definition of non-communicable lung disease

Understanding the way in which NCD-L are defined and diagnosed is an important precursor to interpreting the literature relating to the epidemiology of these conditions. Both asthma and chronic obstructive pulmonary disease (COPD) are frequently diagnosed solely on reported symptom patterns, particularly in low-income settings. However, characteristic spirometric abnormalities form part of the internationally recognised diagnostic gold-standards.[44,45]

NCD-L can be subdivided broadly into obstructive and restrictive lung disease, based on lung volume measurements made using a spirometer: the volume than can be forcibly expired in one second (Forced Expiratory Volume in 1s or FEV_1) and the overall expired volume (Forced Vital Capacity or FVC) following a maximal inspiration. Obstructive lung disease is defined by a reduced ratio of FEV_1 to FVC, and restrictive lung disease by a low FVC.

2.1.1 Asthma: disease definition – clinical setting

Symptom history is central to defining asthma in both clinical and epidemiological settings.[46]

According to Global Initiative for Asthma (GINA) clinical recommendations, asthma diagnosis should be based on characteristic symptoms; cough, wheeze, shortness of breath, chest tightness, and evidence of variable airflow limitation.[44] Airflow variability may be demonstrated by diurnal or day-to-day variation in lung function, bronchodilator reversibility or a positive exercise challenge test or bronchial challenge test. All of these tests require a measure of expiratory airflow; in low-resource settings, the World Health Organization (WHO) recommends peak expiratory flow (PEF) meters, as a potential low-cost alternative to spirometry.[47] Asthma is often associated with airway hyperresponsiveness and airway inflammation, but these are not necessary to make the diagnosis.[44] Once diagnosed, asthma symptoms are monitored using a variety of assessment tools, discussed further in section 2.4.1

2.1.2 Asthma: disease definition – epidemiological setting

The requirements of diagnostic tools used to screen large community populations in epidemiological surveys, are different to the more focused approach described above, required in a clinical setting. Community prevalence surveys commonly rely on a questionnaire-based definition of asthma to describe the burden of symptoms.[48] This approach has limitations; understanding of words such as “wheeze” and “asthma” is not straightforward, and appropriate translation into local languages may be difficult.[49] There is often a discrepancy between wheeze as assessed by parents, compared to clinicians.[50] However, evidence supports the use of a symptom questionnaire alone as a highly valid method to identify asthma in epidemiological prevalence surveys.[46]

The largest asthma prevalence survey in children to date is the International Study of Asthma and Allergy in Children (ISAAC) and the ISAAC questionnaires are widely used in asthma research. ISAAC used a broad question: “Have you had wheezing or whistling in the chest in the last 12 months?”, to assess asthma symptom prevalence (current wheeze). Severe asthma was defined as children with current wheeze and; ≥4 attacks of wheeze, or ≥1 night per week

sleep disturbance from wheeze, or wheeze affecting speech, in the past 12 months (Figure 2-1). [51]

1. Have you ever had wheezing or whistling in the chest at any time in the past? *If no, skip to question 6*
2. Have you had wheezing or whistling in the chest in the last 12 months? *If no, skip to question 6*
3. How many attacks of wheezing have you had in the last 12 months?
4. In the last 12 months, how often, on average has your sleep been disturbed due to wheezing?
5. In the last 12 months, has wheezing ever been severe enough to limit your speech to only one or two words at a time between breaths?
6. Have you ever had asthma?
7. In the last 12 months, has your chest sounded wheezy during or after exercise?
8. In the last 12 months, have you had a dry cough at night, apart from a cough associated with a cold or chest infection?

Figure 2-1. Core questionnaire wheezing module for 13-14-year olds.
From ISAAC survey [52]

2.1.3 COPD: disease definition

COPD diagnosis is also based on typical symptoms; difficulty breathing, chronic cough or sputum production, associated with airflow obstruction. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy states that spirometric assessment, with a post-bronchodilator $FEV_1/FVC < 0.70$ is an essential part of making a diagnosis of COPD.[45] Furthermore, spirometry is used to classify the severity of airflow limitation in COPD (Table 2-1).

Table 2-1. GOLD classification of COPD severity.

In patients with $FEV_1/FVC < 0.70$:		
GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	Very Severe	$FEV_1 < 30\%$ predicted

There is debate as to whether it is preferable to use the lower limit of normal (LLN), which defines the lowest 5% of the non-smoking, asymptomatic population, as a cut-off for diagnosis, rather than a fixed FEV_1/FVC ratio of <0.70.[53] The FEV_1/FVC ratio falls with age, and so the use of a fixed value will incorrectly classify older adults, with normal age-associated changes, as abnormal. Use of a fixed ratio will also underestimate COPD prevalence in adults <45years – this is particularly important in LIC where younger people constitute a greater proportion of the overall population.[54]

It is recognised that patients diagnosed with COPD, using a broad spirometry-based criteria, will encompass heterogenous airways disease, including three major sub-phenotypes; small airways obstruction, emphysema and chronic bronchitis.[55] Airway obstruction results from smooth muscle contraction, mucus hypersecretion, and alveolar-tissue breakdown, with loss of elastic recoil: this leads to a progressive deterioration in lung function in many patients.[56]

2.1.4 Asthma-COPD overlap

The categorisation of patients into distinct clinical groups is not always straightforward; asthma and COPD are heterogenous conditions, with overlapping symptoms. GINA recommend the term “asthma-COPD overlap”, to describe patients who have features consistent with *both* asthma and COPD. In asthma-COPD overlap there is persistent airflow limitation between symptoms, which is not reversible with bronchodilators. The research relating to asthma-COPD overlap is limited: careful clinical characterisation of patients in clinical trials is required to inform individual patient management.[56]

2.1.5 Lung function testing in asthma and COPD

Spirometry is the gold standard for measuring airflow limitation. FEV_1 is reduced in airflow limitation – however this may be found in many other lung diseases and also with poor spirometric technique. A reduced FEV_1/FVC ratio is a more accurate assessment of airway obstruction, and the values obtained should be compared to age-specific predicted values.[57] Repeated measurement, 10-15 minutes after administration of a rapid acting

bronchodilator (e.g. 200-400 µg Salbutamol) is used to demonstrate "reversibility": defined in children as an improvement in FEV_1 of >12% predicted value, and in adults as an increase in FEV_1 of >12% and >200ml from baseline value.[44]

Spirometry should be performed by experienced technicians according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[58] Subjects are instructed to take a deep breath, blow out as hard and fast as they can, and keep blowing. The quality of spirometry traces is highly dependent on the skill of the technician - the use of simple instructions, emphasized with exaggerated body language, is important for all age groups.[59]

The crucial role spirometry plays in the diagnostic work-up and monitoring of asthma and COPD is problematic in resource poor settings, where there is limited access to spirometry or even peak flow monitoring. Estimates of disease prevalence are commonly extrapolated from research projects, rather than population-level surveillance data.[60]

2.1.6 Reference ranges for normal lung function

There are a number of reference ranges, against which measured lung function can be compared. The National Health and Nutrition Examination Survey (NHANES) III has been used extensively to calculate predicted lung function values, by studies including the Burden of Obstructive Lung Disease (BOLD) Initiative: this survey included white individuals, African Americans and Mexican Americans living in the USA.[61] The Global Lung Initiative (GLI) 2012 equations are preferred for younger (<8 years) and older (>65 years) patients and may be a better comparator for patient populations outside of the USA. [57,62] The GLI reference equations were derived using lung function data from healthy individuals, aged 3-95 years, from a variety of ethnic groups; Caucasians (n=57395), African-Americans (n=3545), North-East Asians (n=4992) and South-East Asians (n=8255). The dataset included 33 countries, however sSA was under-represented, with only South Africa included.[57]

Hence the African-American reference ranges are largely derived from individuals living outside of the African continent.

The Prospective Urban and Rural Epidemiological (PURE) study analysed pre-bronchodilator spirometry from healthy people aged 34-80 years, with <5 pack-year smoking histories from 17 countries.[63] Participants living in sSA (from South Africa and Zimbabwe) had lower age-, height- and sex-adjusted FEV_1 and FVC values; by 20.9% (95% CI 19.9-22.0) and 24.3% (95% CI 23.3-25.4) respectively, than those living in North America or Europe. Those from sSA (n=799) included 99.6% black Africans, 54.9% from urban communities, and 71.1% females. Absolute lung function measurements were; mean (SD) FEV_1: 1.98L (0.50) for women, 2.65L (0.72) for men; mean (SD) FVC: 2.33L (0.58) for women, 3.16L (0.84) for men. The mean (SD) body mass index (BMI) for the sSA women was 30.1 (7.9) kg/m^2 indicating considerable overnutrition, which would be unexpected in many communities from LIC in sSA and hence limits the generalisability of the data. Studies of urban and rural populations in Malawi reported rates of obesity (BMI>30) of 13% and 3%, respectively.[22,23]

Some authors have derived local reference ranges from symptom-free non-smoking study participants.[22,64,65] However, this normalises the impact of local environmental factors, such as nutrition, infections and pollutants, which may determine lung function. A local reference range is therefore unlikely to represent the best possible lung function attainable for an individual, had they experienced ideal conditions for lung growth and development.[66]

2.2 Prevalence of non-communicable lung disease in sSA

2.2.1 Children

Among children, asthma is the most common chronic disease and is an emerging public health problem in Africa, where children account for a high proportion of the total population.[20,67] The majority of data relating to global asthma prevalence is from the International Study of Asthma and Allergies in

Children (ISAAC) - the most comprehensive, international survey of childhood asthma prevalence to date. Phase 1 (1992-1996) used core questionnaires to assess the prevalence and severity of asthma and allergic disease and this was repeated in phase 3 (2000-2003) to assess prevalence trends.[52,68]

During Phase 3, 22 centres were enrolled from 16 African countries, including; Morocco, Tunisia, Democratic Republic of Congo, Togo, Sudan, Cameroon, Gabon, Reunion Island, South Africa, Algeria, Kenya, Ethiopia, Ivory Coast, Nigeria, Congo, and Sudan.[67] The prevalence of "current wheeze" among 13-14 year old children from these countries is shown in Figure 2-2.

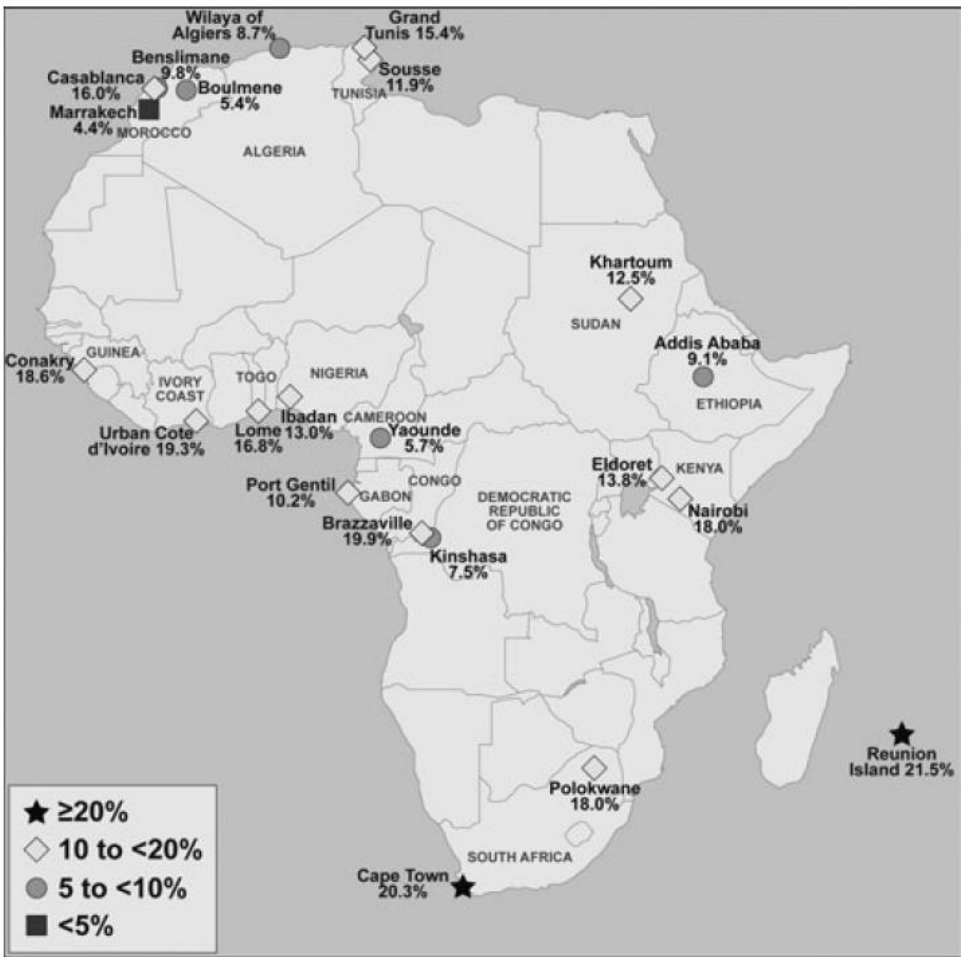

Figure 2-2. Prevalence of symptoms of wheeze in the past 12 months, 13-14-year age group.

From ISAAC Phase 3: Ait-Khaled et al.[67]

Four urban sites from southern Africa; Eldoret and Nairobi (in Kenya) and Cape Town and Polokwane (in South Africa), reported the prevalence of

"current wheeze" as 14-20%, with severe asthma symptoms in 4-7% of children aged 13-14 years.[67]

Only two sub-Saharan African sites included children aged 6-7 years, with reported "current wheeze" in 6% in Ibadan, Nigeria, and 13% in Polokwane, South Africa. Subsequent studies, adopting ISAAC methodology to explore prevalence in the younger age group, reported rates of current wheeze of; 16% in Gaborone, Botswana; 5% in Lusaka, Zambia and 13% in Maputo, Mozambique: all urban sites.[69-71] Only one study has reported asthma prevalence in younger children from a rural African setting; in Niakhar, Senegal, 9% had current wheeze, and 5% severe wheeze.[72]

Table 2-2 details studies from sSA, published from 2000 onwards, reporting either asthma or exercise-induced bronchoconstriction (EIB) prevalence rates among school-aged children. One of the challenges in comparing these data is the variety of definitions used, both the define asthma and EIB.

Table 2-2 Studies from sub-Saharan Africa reporting prevalence of asthma or exercise induced bronchospasm in school-aged children from 2000 onwards

Author and publication date	***Country and rural/urban location***	***Number of subjects***	***Age (years)***	***Method of assessment***	***Prevalence of asthma indicator***
Perzanowski, 2002[73]	*Thika town / Kabati village, Kenya* Urban / Rural	265	8-15	Questionnaire, 6-min exercise test (15% fall in FEV_1)	EIB: 12% urban, 11% rural Asthma history: 10% urban, 4% rural
Steinman, 2003 [74]	*Cape Town/Transkei, South Africa* Urban/peri urban/rural	1457	10-14	Histamine challenge, skin prick test, questionnaire	BHR: 17% rural Xhosa, 34% urban Xhosa, 33% urban white
Hailu, 2003 [75]	*Gondar town, NW Ethiopia* Urban	3365	13-14	ISAAC I	Current wheeze: 16% Severe 5%
Mavale-Manuel, 2004 [76]	*Maputo, Mozambique* Urban, suburban, semi-rural	2383 2630	6-7 13-14	ISAAC	Current wheeze: 13.3% in both age groups
Davey, 2005 [77]	*Butajira, Ethiopia* Urban / rural	1158 2645	5-9 10-19	Questionnaire, skin prick test	Current wheeze: 8-9%, both age groups
Mashalane, 2006[78]	*Thokoza, South Africa* Urban Poor	495	9-10	Questionnaire, 6-min exercise test (15% fall in PEFR)	EIB: 7.3%
Addo-Yobo, 2007 [79]	*Kumasi, Ghana* Urban rich, urban poor, rural	1848	9-16	Exercise challenge (12.5% fall PEFR), skin prick test	EIB: 8.3% urban rich, 3.0% urban poor, 3.9% rural

BHR, bronchial hyperreactivity; EIB, exercise induced bronchoconstriction; FEV_1, forced expiratory volume in 1 second; ISAAC, International Study of Asthma and Allergies in Childhood; PEFR, peak expiratory flow rate

Table 2.2 continued

Author and publication date	***Country and rural/urban location***	***Number of subjects***	***Age (years)***	***Method of assessment***	***Prevalence of asthma indicator***
Berntsen, 2009 [80]	*Manyara region, Tanzania* Rural	172	9-10	ISAAC - video	Current wheeze 12%, severe 5%
Calvert, 2010[81]	*Khayelitsha settlement and Kentani district, South Africa* Urban / Rural	3322	8-12	6-min exercise test (15% fall in FEV_1), skin prick test, IgE	EIB: 14.9% urban, 8.7% rural
Hooper, 2012[72]	*Niakhar, Senegal* Rural	1513	5-8	ISAAC - written	Current wheeze 9% Severe 5%
Adetoun Mustapha, 2013[82]	*Warri and environs, South Nigeria* Rural/urban	1397	7-14	ISAAC - written	Current wheeze 5.7% urban, 4.1% rural
Oluwole, 2013[83]	*Ibadan / Abanla; Eruwa; Igbo-Ora, Nigeria* Urban / Rural	1736	13-14	ISAAC questionnaire, skin prick test, serum eosinophils, IgE	"Asthma" 7.5% rural, 8.0% urban
Shimwela, 2014[84]	*Ilala / Bagamoyo districts, Tanzania* Urban / Rural	1229	Mean (SD) 16.8 (1.8) y	ISAAC questionnaire	Current wheeze: 23.1% urban, 12.1% rural
Wa Somwe, 2015 [69]	*Lusaka, Zambia* Urban	2026 1885	7-8 13-14	ISAAC - written	Current wheeze: 5% age 7-8, 8% age 13-14
Kiboneka, 2016[70]	*Gabarone, Botswana* Urban	358 817	6-7 13-14	ISAAC - written	Current wheeze: ~16% both ages, severe ~5%

BHR, bronchial hyperreactivity; EIB, exercise induced bronchoconstriction; FEV_1, forced expiratory volume in 1 second; ISAAC, International Study of Asthma and Allergies in Childhood; PEFR, peak expiratory flow rate

Authors have proposed that EIB provides a more objective measure of asthma than questionnaire data, particularly in settings where questionnaire responses may be unreliable due to cultural and linguistic reasons.[79] However, studies which have reported both EIB and asthma symptom prevalence demonstrate that using EIB as a proxy for asthma will overestimate the true burden of asthma symptoms.[73,85] A study of Kenyan school children reported EIB rates of 11% and 12% in rural-dwelling and urban-dwelling children, respectively.[73] Of these 30 children with EIB, only six (20%) reported a history of symptoms or medication use consistent with a diagnosis of asthma.

A study in Cape Town, South Africa, reported overall EIB rates of 5% among randomly selected school children.[85] Questionnaire data was also used to identify children with asthma, based on previous episodes of airflow obstruction with a positive response to bronchodilator treatment. Using this definition of asthma, EIB had a sensitivity of 0.31, and specificity of 0.97. The use of EIB as a community screening tool for asthma is likely to identify many children who do not have symptomatic asthma. However, it may be a useful test to support diagnosis in those who have presented with symptoms.

Among children worldwide with current wheeze, those from Africa showed the highest prevalence (51%) of severe symptoms, defined as; ≥4 attacks, or wheeze disturbing sleep at least once weekly, or speech-limiting wheeze, in the past 12-months.[51] The clinical significance of "current wheeze" is debatable, particularly given the frequency of episodic wheeze induced by viral infections in children. However, sleep-disturbing or speech-limiting attacks are clinically important and are highly specific for airway hyper-responsiveness assessed by methacholine challenge.[49]

2.2.2 Adults

Data regarding asthma in Africa is limited, with most research focusing on a few countries (particularly South Africa and Nigeria).[86] However, increasing prevalence has been reported over the past twenty years, with an estimated 119.3 million cases (12.8% prevalence) of asthma in Africa in 2010.[87]

Estimates of global asthma prevalence in adults have been derived from the WHO World Health Survey, the only standardised global data on asthma symptoms and diagnosis in adults, conducted between 2002-2003. [88,89] In Africa, the prevalence of self-reported wheeze in the past year ranged from 4.8% (in Mali) to 15.4% (in Swaziland), with an average of 7.7%. The prevalence of doctor-diagnosed asthma was lower: 3.9% on average. The prevalence of wheezing in the past year and doctor-diagnosed asthma in Malawi were 7.8% and 4.6%, respectively.[89]

A systematic review of COPD-related data from sSA published before 2011 reported COPD prevalence varying between 4-25%.[60] However, of the nine studies included, only two (relating to the same dataset from South Africa) used robust population sampling and diagnostic methods.[60,90]

The Burden of Obstructive Lung Disease (BOLD) Initiative, using standardised post-bronchodilator spirometry with quality control, has conducted studies in South Africa, Nigeria, Malawi and Tanzania.[22,23,90-92]

Table 2-3 presents these BOLD studies, and others from sSA that have described obstructive and restrictive spirometric patterns, using post-bronchodilator spirometry, with representative population sampling.

A high prevalence of moderate to severe obstruction in adults aged >40 years has been reported in Cape Town, South Africa (19.1%) compared to 7.0% in Blantyre, Malawi, and 7.7% in Ife-Ife, Nigeria.[22,90,91] High rates of cigarette smoking were reported in South Africa (83% men and 59% women "ever smokers"), compared to 10% in Malawi and 11% in Nigeria which may explain the observed differences in obstruction. A more recent BOLD study from Tanzania reported an overall COPD prevalence rate of 17.5%, with moderate-severe obstruction in 10.9%: 25.2% of participants reported "ever-smoking", including 5.4% "current smokers".[92]

The FRESH-AIR study in Masindi district, rural Uganda, reported a prevalence of COPD of 16.2%, defined as an FEV_1/FVC <LLN (using European Community for Steel and Coal/European Respiratory Society reference ranges[93]), or 12.4%

based on the fixed GOLD criteria.[94] However, this COPD prevalence includes GOLD stage 1; 3.6% of participants were categorised as having GOLD stage 2 or greater, which is in keeping with subsequent studies in Uganda reporting prevalence ranging from; 1.7% in urban Kampala, 7.4% in rural Nakaseka and 3.3% in rural Mbarara.[95,96]

The comparison of global COPD literature is challenging due to differences in diagnostic criteria (FEV_1/FVC <LLN threshold or fixed ratio), reference ranges used (NHANES, GLI, local) and age ranges of participants.[54] To summarise the data presented in Table 2-3, the prevalence of moderate to severe airway obstruction in sSA countries is relatively low, ranging from 3.3 - 10.9%, with the exception of South Africa. A systematic review and meta-analysis of global COPD prevalence in 2010 reported rates of 15.2% in the Americas, 13.2% in the Eastern Mediterranean region and 12.0% in Europe.[97] Within this review, of 140 study sites, there were only six studies from Africa, and only 2 studies which performed post-bronchodilator spirometry.[97,98]

A strong positive association between airflow obstruction and pack-years smoked, has been demonstrated across all the BOLD sites.[24] However, high mortality rates are associated with spirometric restriction (reduced FVC), rather than obstruction, and this is seen in poorer countries, where smoking is far less prevalent.[24]

The prevalence of spirometric restriction reported in studies, is highly influenced by the chosen population reference range.[66] The third US National Health and Nutrition Examination Survey (NHANES III) Caucasian range, has been used across the BOLD research centres, for consistency, and to permit comparison of study sites.[61] Using this reference population, reported rates of restrictive spirometry are; 39% and 35% in urban and rural Malawi, respectively; 70% in Ife-Ife, Nigeria; 46% in Cape Town, South Africa.[22,24,64] However, when locally derived reference comparisons are made, the rates of decreased FVC are much lower; at 9% in Malawi and approximately 3% in Nigeria.[22,64]

Table 2-3 Studies from sub-Saharan Africa assessing post-bronchodilator lung function in adults

Author, date, country	*Study population*	*Sample size*	*Spirometry reference range*	*Results*
Buist, 2007[90] Multi-site; South Africa (urban)	Age ≥40y, random sample from population (BOLD)	847	NHANES III (Caucasian)[61]	COPD: GOLD Stage 2: 19.1% for South Africa
Musafiri, 2011[65] Rwanda (urban/rural)	Aged ≥15y, systematic sampling from population registers	1824/2138 with acceptable spirometry	Local reference ranges*	14% FEV_1/FVC<LLN, post bronchodilator: asthma 8.9%; COPD 4.5% overall, 9.6% ≥45y
Pefura-Yone, 2016[99] Cameroon (urban)	Aged ≥19y, random population sampling Note: 70% <40y age	1287/1612 with acceptable spirometry	Reference range derived by Musafiri for Rwandan population[65]	FEV_1/FVC<LLN 3.8%, post bronchodilator FEV_1/FVC<LLN 2.4%
Van Gemert, 2016[94] Uganda (rural)	Aged >30y, random sampling of 20 households/village	588/620 with acceptable spirometry	African and Indian estimates from ECSC/ERS 1993[93]	COPD (FEV_1/FVC<LLN); 16.2% overall, 3.6% GOLD2+ 12.4% (FEV_1/FVC<0.7)
Meghji, 2016[22] Malawi (urban)	Aged ≥18y, age- and sex-stratified random sample from population (BOLD)	749/1059 with acceptable spirometry	NHANES III (Caucasian), local reference ranges*	Restriction (FEV_1/FVC>0.7 and FVC<80% predicted): 38.6% NHANES, 9.0% local Obstruction GOLD2+: 3.6% overall, 7.0% in ≥40y
Obaseki, 2016[91] Nigeria (suburban)	Aged ≥40y, random sample from population (BOLD)	883/1169 with acceptable spirometry	GLI 2012 (African Americans)[57], NHANES III (Caucasian), local reference ranges*	Post BD FEV_1/FVC<LLN 7.7% (GLI), 6.9% (NHANES), 3.5% (local)
Obaseki, 2017[64] Nigeria (suburban)	As above	As above	As above	Restriction (FVC<LLN); NHANES 70.4% M, 72.8% F; GLI 15.5% M, 20.5% F; local 3.0% M, 3.5% F

Author, date, country	*Study population*	*Sample size*	*Spirometry reference range*	*Results*
Magitta, 2018[92] Tanzania (rural)	Aged ≥35y, random population sample (BOLD)	496/869 with acceptable spirometry	Unclear from methods	COPD 17.5% overall (post BD FEV_1/FVC <0.7); 10.9% GOLD2+. Restrictive pattern 9.8%.
Nightingale, 2019[23] Malawi (rural)	Aged >18y, age and sex stratified random sample from population (BOLD)	886/1481 with acceptable spirometry	NHANES III (Caucasian)	Obstruction (FEV_1/FVC<LLN) 8.7%, restriction (FEV_1/FVC>0.7 or LLN and FVC <80% predicted) 34.8%
North, 2019[95] Uganda (rural)	Aged ≥18y, from enumerated population, attending health screening event	565/843 with acceptable spirometry	NHANES III (African American)	COPD (post BD FEV_1/FVC<LLN) 2.3% overall, 3.3% in ≥40y

*Local reference ranges generated from subset of asymptomatic, non-smoking study participants

BD: bronchodilator; BOLD: Burden of Obstructive Lung Disease study; COPD: Chronic Obstructive Pulmonary Disease; ECSC/ERS: European Community for Steel and Coal/European Respiratory Society; FEV_1: Forced Expiratory Volume in 1s; FVC: Forced Vital Capacity; GLI: Global Lung function Initiative; LLN: lower limit of normal; NHANES III: National Health and Nutrition Examination Survey

2.2.3 Urban-rural differences

In the last twenty years, Africa has experienced a rapid rate of urban growth. By 2025, it is estimated that more than half of the population of Africa will live and work in urban centres.[100] Asthma is more prevalent in urban than rural populations: a recent meta-analysis of studies from LMICs reported a higher prevalence of asthma in urban settings, regardless of the way in which asthma was defined.[101]

As a growing proportion of the African population is exposed to urban environments, so the prevalence of asthma is expected to rise.[87] Surveys in Ghana, conducted in 1993 and 2003, assessed exercise-induced bronchoconstriction (EIB) in children aged 9-16 years from urban rich, urban poor and rural schools.[79] Over ten years, EIB doubled across all sites, with an overall increase from 3.1% (95% Confidence Interval (CI): 2.2-4.3%) to 5.2% (95% CI: 4.3-6.3%). Sensitisation, particularly to cat and dog, also increased significantly (from 7.6% (95% CI: 6.1-9.5%) to 13.6% (95% CI: 12.1-15.3%) with EIB and sensitisation more common in those children from urban rich schools.

Table 2-2 includes some studies where an urban-rural comparison has been made. These data show an increased rate of asthma symptoms or EIB in urban-dwelling children in Ghana, Kenya, Tanzania and South Africa.[73,79,81,84] However, studies from Nigeria and Mozambique did not detect such differences.[76,82,83]

Urbanisation is clearly an important determinant of asthma prevalence, but the simple urban-rural categorisation does not permit a deeper understanding of the lifestyle or socioeconomic factors which might cause this.[101] Furthermore, there is no agreed operational definition of “urban” or “urbanisation” to facilitate meaningful comparison or pooling of data.

It has been proposed that childhood infections are less frequent in urban settings due to improved personal and public hygiene, and increased access to health care and use of antibiotics. However, in rapidly growing cities, living

conditions in some areas may be inferior to that in rural areas, with widespread poverty, inadequate housing, infrastructure, and poor access to services.[102]

Urbanisation is also associated with increased environmental pollution, a more sedentary lifestyle, unhealthy "processed" diets and obesity; these factors are all linked to increased risk of asthma.[103,104] Studies from high-income countries (HIC) have demonstrated decreased prevalence of asthma and atopy among children raised in rural, farming environments.[105] Early exposure to animals, consumption of unpasteurised farm milk, and high levels of endotoxin (a proxy for microbial exposure) have been associated with decreased asthma and atopic diseases. Studies of children from Amish traditional farming communities reveal extremely low rates of asthma, high levels of endotoxin exposure and differences in innate immune profiles, when compared to children from alternative farming communities in the USA.[106] Strachan's original "Hygiene Hypothesis" proposed that early life infections might contribute to the development of the immune system and protect against allergic disease.[107] However, the complex balance between microbe-driven proinflammatory, type-1 T-helper cell innate immune responses and allergen-driven proallergic, type-2 T-helper cell adaptive immune responses are yet to be fully understood.[108,109]

2.3 Non-communicable lung disease across the life course

2.3.1 Lung development: airway and alveolar growth

Human fetal lung development occurs in five phases (Table 2-4) with formation of the conducting airways and alveoli, essential components for effective *ex-utero* gas-exchange, by the end of a full-term pregnancy.[110]

Table 2-4. Phases of *in-utero* lung development

Synthesized from Copland 2004, and Stocks 2013[110, 111]

Embryonic phase 4-7 weeks' gestation	Lung buds develop
Pseudoglandular phase 7-16 weeks' gestation	Conductive airway pattern develops Early airway epithelium differentiation
Canalicular phase 17-26 weeks' gestation	Completion of airway branching Development of gas-exchange region
Saccular phase 27-36 weeks' gestation	Growth and maturation of peripheral airways, differentiation of alveolar epithelial cells and maturation of surfactant system
Alveolar phase 34 weeks' gestation to adolescence	Increase in alveolar number and subsequent increase in gas exchange area

Timings are approximate and there is overlap between developmental phases

By the start of the third trimester of pregnancy (27-weeks' gestation), airway branching is completed, the gas-exchange region is developing, and surfactant production has begun. Subsequently, there is further growth of the pulmonary parenchyma and maturation of the surfactant system. From approximately 32-weeks' gestation, there is rapid expansion of alveolar numbers and resulting lung growth, which continues postnatally during the first 2 years of life. Stereological assessment of lungs from human autopsies and studies using helium-3 magnetic resonance to assess alveolar size, suggest that neoalveolarization continues throughout childhood and adolescence.[112,113] After this point, alveolar size continues to increase with somatic growth but alveolar numbers remain constant, at around 300-600 million.[114] There is some evidence that lung growth is possible in adulthood, through expansion of alveolar numbers, under specific circumstances (post-pneumonectomy).[115]

In comparison to alveolar development, which is predominantly a postnatal process, airway development in largely completed by birth. Airway branching is completed by 17 weeks' gestation, following which there is increasing vascularisation, and enlargement of the airway lumen, with reduction of

connective tissue (the canalicular phase).[116] Airway growth, with increasing airway diameter and length, continues to a plateau at 20-25 years of age, with gradual decline thereafter.[57]

Insults to the lungs at any point across the life course have the potential to disrupt the normal stages of growth and development. Repair of damaged airways, known as pathological remodelling, can affect various airway elements, including the epithelium, smooth muscle cells, extracellular matrix, nerve tissue and vasculature.[117] In asthma, the changes typically involve thickening of the reticular basement membrane, increased airway smooth muscle mass, angiogenesis and goblet cell hyperplasia.[118] COPD is associated with a thickened airway smooth muscle layer, with disproportionate increase in extracellular matrix, enlargement of submucosal mucous glands with hypersecretion, and destruction of the peripheral airways.[119]

Pathological remodelling can develop during early childhood. Bronchial reticular basement membrane thickening and eosinophilic inflammation are absent in wheezy infants with reversible airflow obstruction: however, these abnormalities were identified in a group of children (median age 29-months) with severe pre-school wheeze.[120,121]

The early life origins of lung function and respiratory disease have been established in several longitudinal cohort studies, all conducted in HIC.[111] Meta-analysis of 25,000 children from 24 birth cohorts, reported that prematurity, low birth weight and greater infant weight gain were associated with an increased risk of childhood asthma.[122] The Tucson Children's Respiratory Study described symptom patterns in early childhood; transient early wheeze (present before age 3 years, but not at 6 years), persistent wheeze (present before age 3 years and at age 6 years) and late-onset wheeze (no wheeze before age 3 years, but present at 6 years). Children with persistent wheeze show substantially lower FEV_1 at age 6 years, compared to transient early wheezers.[123] Follow-up of this cohort found that wheezing at age 6 years (whether persistent or late-onset), was associated with continuing symptoms at age 16 years, and that deficits in lung function are present by

age 6 years, with little change thereafter.[29] Furthermore, children with wheeze before the age of 3 years demonstrate decreased lung function in early childhood, which persists throughout adolescence, even in the absence of continued wheezing symptoms.[29]

Late-onset or persistent wheeze, or bronchial hyperreactivity in the absence of symptoms at age 6 are strong predictors for both chronic and new-onset asthma in adults.[32]

Cohort studies from Dunedin, New Zealand and Melbourne, Australia, also reported tracking of lung function, with lung function following centiles set in early childhood throughout later childhood and adulthood, regardless of asthma severity.[31,34]

The Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) followed "at-risk" infants of asthmatic mothers, and reported that children who developed asthma symptoms by age 7-years had significant airflow deficits and bronchial hyperresponsiveness as neonates.[124]

The Drakenstein Child Health Study (DCHS) in South Africa, will provide data of greater relevance to populations in sSA, as their cohort ages. This is particularly important as potential risk factors for adverse lung health outcomes vary between high- and low-income settings, with determinants such as prematurity and low birth weight, *in-utero* HIV-exposure, early life LRTI and exposure to indoor air pollution more common in LIC.[125-128]

2.3.2 Determinants of respiratory health

Factors affecting the lungs during critical periods of growth and development, both before and after birth, may have a long term impact on lung health in adulthood.[114] In a low-income setting such as Malawi, prenatal risk factors such as poor maternal nutrition and *in-utero* exposure to particulate matter are commonly encountered. Low birth weight (LBW), due to premature delivery, suboptimal intrauterine growth, or a combination of the two, is associated with worse adult lung function.[129] Postnatally, poor nutrition,

exposure to air pollutants, and respiratory infections, including tuberculosis (TB) and HIV-related infections, are of particular concern.

2.3.2.1 *Maternal exposure to inhaled pollutants during pregnancy: tobacco smoke, household and ambient air pollution*

There is strong evidence from HIC that *in utero* exposure to tobacco smoke is associated with reduced respiratory function in the early neonatal period, and increased prevalence of respiratory infections and asthma.[130,131] The South African DCHS reported altered lung function at age 6-10 weeks in infants of maternal smokers, and increased wheeze and lower respiratory tract infection (LRTI) at age 1-year.[125,127] Tobacco smoke contains thousands of chemicals, of which nicotine is thought to be a key mediator of altered pulmonary function. Nicotine exposure is unlikely to be a major problem in Malawi, where rates of maternal smoking are low, but impaired lung development may also result from hypoxaemia, secondary to carbon monoxide (CO). High levels of carbon monoxide are found in cigarette smokers and are also seen in those using biomass fuels to cook in low-income settings.[23] The effect of *in utero* household air pollution, from incomplete combustion of biomass fuels, on fetal lung development is largely unknown. Recent work from Ghana described an association between *in utero* household air pollution exposure and impaired infant lung function, at 30 days of age.[40] In South Africa, antenatal exposure to the volatile organic compound toluene was associated with severe LRTI in infants; further research on this kind of exposure in early life is needed.[127]

A few studies from high-income settings have explored the impact of air pollution exposure during pregnancy and postnatal lung function.[132] One study measured lung function at 5 weeks of age and found altered lung function associated with higher maternal exposure to particulate matter ≤10µm (PM_{10}), particularly during the last trimester of pregnancy.[133] Clinically significant lung function impairment at preschool age has been associated with higher levels of maternal exposure to outdoor air pollution (benzene, nitrogen dioxide (NO_2) and fine particulate matter ≤2.5µm ($PM_{2.5}$)) during

pregnancy.[134,135] A population based nested case-control study reported an increased risk of asthma diagnosis with increased exposure to pollutants (CO, nitrogen oxides, PM_{10} and sulphur dioxide (SO_2)) *in utero* and during the first year of life, with the strongest effects noted for traffic-related pollutants.[136]

2.3.2.2 *Maternal nutrition during pregnancy*

Modification of maternal nutrition has been suggested as a potential strategy in the primary prevention of asthma, with particular interest in maternal intake of vitamins D, E and omega-3 polyunsaturated fatty acids (PUFAs) during pregnancy.[137,138]

Vitamin D is reported to have antimicrobial, antiviral and anti-inflammatory activity; vitamin D supplementation of known asthmatic patients has been found to decrease the rate of exacerbations requiring oral corticosteroids.[139,140]

Observational studies exploring the role of maternal nutrition on childhood respiratory outcomes have suggested that higher intake of vitamins D, E and zinc during pregnancy is associated with a decreased risk of wheezing during the first 5 years of life.[141,142] A large UK-based birth cohort study (n=8915) reported a beneficial effect of maternal zinc intake during pregnancy on lung function at age 7-9 years but no effect on asthma diagnosis, and found no association between other antioxidants, including vitamin E, and asthma or lung function.[143] Although randomised-controlled trials (RCTs) from Denmark (Copenhagen Prospective Studies on Asthma in Childhood: COPSAC) and USA (Vitamin D Antenatal Asthma Reduction Trial: VDAART) suggested that high dose vitamin D_3 supplementation during the second and third trimester of pregnancy might protect against wheeze at age 3 years, neither trial found an effect on asthma diagnosis at age 6 years. [144-146]

The COPSAC group also conducted an RCT (n=736) of n-3 long-chain PUFA supplementation during the third trimester of pregnancy. A 31% risk reduction for persistent wheeze at age 3-5 years was seen in children of

mothers receiving supplementation, with the greatest effect seen in mothers with the lowest blood levels of long-chain PUFAs at randomisation.[147]

There has been no research to date on maternal micronutrient status and respiratory outcomes in LIC. However, a recent systematic review and meta-analysis reported a high prevalence of vitamin D deficiency across the African continent, with women and newborns at particular risk.[148]

Considering maternal nutritional intake more broadly, maternal undernutrition and subsequent fetal undernutrition leads to intrauterine growth restriction (IUGR).[149] The effects on lung structure depend on the gestational timing and severity of IUGR; potential mechanisms include impaired alveolarization, thickening of inter-alveolar septa due to increased extracellular matrix deposition, and thickening of the alveolar blood-air barrier due to increased basement membrane thickness.[150,151] IUGR, which may also result from non-nutritional factors, is discussed further in section 2.3.2.3.

2.3.2.3 *Low birth weight and prematurity*

Low birth weight (LBW) – a birth weight of <2500g - may be due to IUGR, premature delivery (before 37-weeks' gestation) or both. Premature delivery and IUGR are more common in LICs; in sSA approximately one in eight infants are born early and Malawi has the highest rate of premature birth (18.1%) in the world.[152] Young maternal age and short inter-pregnancy intervals are common risk factors contributing to premature delivery and IUGR. Poor maternal nutrition, intrauterine and systemic infection (e.g. malaria and syphilis), and physical labour during pregnancy may precipitate early labour, while low maternal weight, hypertensive disorders of pregnancy, and congenital infections (e.g. cytomegalovirus, HIV, syphilis and malaria) are associated with IUGR.[153,154,155] Meta-analysis of studies from HIC found a strong association between birth weight and adult FVC; with 60ml higher FVC in adulthood per kg increase in birth weight (95% CI: 43-76ml), but weaker evidence for airflow obstruction.[156]

A recent meta-analysis of 11 studies conducted in HIC, found that infants born <32 weeks' gestation or with a birth weight <1500g had decreased airflow in late adolescence and early adulthood, with a mean difference in FEV_1 z-score of -0.78 (95% CI: -0.96 - -0.61) compared to infants born at term or with normal birthweight.[157] The infants included in these studies were born before the early 1990s, when surfactant therapy was not available, as is currently the case in Malawi. Babies with bronchopulmonary dysplasia were found to have worse lung function: however, bronchopulmonary dysplasia is usually seen in infants who have required invasive mechanical ventilation which is not available in low-income countries. Reduced lung function is also seen in infants born moderately to late preterm (i.e. at 32-36 weeks' gestation); a Swedish birth cohort study found no evidence of catch-up lung growth for these children at the age of 16 years.[158]

Due to the lack of intensive neonatal care, babies born very prematurely or with a birth weight of <1000g in Malawi are unlikely to survive.[159] However, there is increasing availability and use of non-invasive continuous positive airways pressure (CPAP) in LMIC hospitals.[160] Low-cost bubble CPAP machines were evaluated on the neonatal ward at Queen Elizabeth Central Hospital in Malawi in 2012; survival rates of infants weighing 1000-1500g were greater in those who received CPAP treatment: 65.5% (95% CI: 47–80%) in the CPAP group compared to 15.4% (95% CI: 4–45%) in the control group (p<0.001).[161] As advances in neonatal care in LMIC result in improved outcomes for LBW and premature infants, it is likely that increasing numbers of survivors will reach adulthood with sub-maximal lung volumes and airflow deficits.

2.3.2.4 *The effect of breastfeeding on lung health*

Human breast milk contains many immunological components, including antimicrobial, anti-inflammatory and immunomodulatory agents.[162] It is widely accepted that breastfeeding reduces morbidity and mortality related to LRTIs.[163,164,165] Meta-analysis of 18 studies estimated that breastfeeding reduces the risk of LRTI by 32% (pooled relative risk (RR) [95% CI] 0.68 [0.60-0.77]), LRTI-related hospital admissions by 57% (pooled RR [95% CI] 0.43

[0.33-0.55]), and LRTI-related deaths by 70% (pooled RR [95% CI] 0.30 [0.16-0.56]).[166]

However, the effect of breastfeeding on the development of wheeze and asthma, is less clear. Results are conflicting, there is heterogeneity of methodology and definitions used, and the ethical problem of conducting RCTs with breastfeeding mothers limits the quality of evidence available. Human milk composition varies within and between mothers, which may also explain conflicting data, particularly relating to breastfeeding and the development of allergic sensitisation and allergic disease.[167] Furthermore the research largely represents populations from HIC: a systematic review of 117 studies included only one study from Africa, and no studies were from LIC.[168] The findings of this systematic review suggested that breastfeeding protects against the development of childhood asthma, with the strongest association seen in children aged 0-2 years old.[168] Another meta-analysis reported decreased asthma at age 5-18 years in breastfed children, with a greater effect seen in LMIC (odds ratio (OR) (95% CI) 0.78 (0.70, 0.88)), however the quality of included studies were suboptimal.[169] Phase 2 of ISAAC reported decreased nonatopic wheeze in children who had been breastfed, with a stronger effect in those from LMIC: adjusted OR (95% CI), 0.69 (0.53-0.90) vs 0.87 (0.72-1.06) for LMIC and HIC, respectively.[170] It seems likely that the major effect of breastfeeding is on respiratory infection induced wheeze rather than atopic wheeze.[167] In addition, the reduction in early life respiratory infections associated with breastfeeding may reduce the subsequent development of asthma.[169] The role of early life respiratory infections and subsequent lung health is discussed further in section 2.3.2.7.

In Malawi, it is recommended that children are exclusively breastfed in the first 6-months of life. In practice however, the rate of exclusive breastfeeding declines with age, as other liquids and complimentary foods, most commonly porridge, are added to the diet. Overall 61% of infants aged below 6-months are exclusively breastfed: 80% at age 0-1 month, 69% at age 2-3 months and 34% at age 4-5 months.[10]

2.3.2.5 *Malnutrition during childhood*

The recent ChroSAM study from Malawi followed children who were admitted to hospital for severe acute malnutrition (SAM) during early childhood.[171] Survivors of SAM had comparable lung function to two control groups (siblings and community controls) at 7-years post-treatment; however 46% of the SAM cases had died before follow-up: these children are likely to have had more severe disease and possibly poorer lung function had they survived.[172] Stunting of somatic growth, with preserved torso height and shorter legs, is seen in survivors of malnutrition and might suggest that lung function could also be preserved.

A cross-sectional study of school-aged children from Angola, Democratic Republic of Congo and Madagascar found reduced FEV_1 and FVC z-scores, but normal FEV_1/FVC ratios, comparing undernourished (BMI z-score <-2) to normally grown children, suggesting decreased lung growth without evidence of airway obstruction.[173]

2.3.2.6 *Exposure to inhaled pollutants during childhood: tobacco smoke, household and ambient air pollution*

Over 90% of the world's population breathe air that fails to meet WHO Air Quality Guidelines, with those from least developed countries worst affected.[174] Inhaled pollutants come from various sources: exposure levels depend on many factors including social habits, domestic fuel use, urbanisation, traffic and transport, power plants and industry, policy and legislation.[175]

There is strong evidence from across the globe, that children exposed to tobacco smoke, from either parent, have an increased risk of asthma.[176] This risk is greatest for children exposed to maternal smoking in the first year of life, highlighting the importance of exposures during early childhood.

Large cohort studies from high-income settings, following children in later childhood, have explored the impact of both regional air quality and local traffic exposure on lung development. Diminished lung function, most notably

FEV_1, was found in children exposed to higher levels of air pollution (particularly NO_2, $PM_{2.5}$, acid vapour and elemental carbon).[177-179] Conversely, long term improvements in air quality, with significantly decreased $PM_{2.5}$ and NO_2, have been associated with positive effects on lung function-growth in older children.[180]

Although it is well established that outdoor air pollution contributes to exacerbations of pre-existing asthma, the association with new-onset asthma is less clear.[104] There is accumulating evidence that ambient air pollution, particularly traffic-related, is associated with incident asthma in children.[136,181-183] However, a meta-analysis of cross-sectional studies comparing communities with different air pollution levels, found no effect of long-term exposure to pollution on asthma diagnoses at community level.[184]

Inhaled pollutants could contribute to the development of asthma through several proposed mechanisms; 1. oxidative stress and airway damage, 2. airway wall remodelling, 3. inflammatory pathways and immunological effects, 4. enhanced respiratory sensitisation to allergens.[185]

Research has tended to focus on individual pollutants, reflecting air quality regulation methodology. However, the health effects of the pollutant mixture may be more relevant.[104] Traffic-related air pollution is a complex pollution mixture containing particulate matter and primary gaseous emissions, including nitrogen oxides: these emissions in turn generate secondary pollutants such as ozone, nitrates and organic aerosols. The concentration of these pollutants decrease with distance from roadways: those living within 300-500m of roadways are at greatest risk of adverse health effects.[186] Consideration of type of traffic, in addition to distance from traffic may also be important: ISAAC reported a positive association between self-reported exposure to truck traffic on the street of residence and asthma symptoms.[187]

Exposure to household air pollution is a major concern in LMICs, where the use of inefficiently burned, highly polluting biomass fuel is common. Biomass is plant or animal material used for energy production, comprising five

primary components: cellulose, hemicellulose, lignin, extractives/volatiles and ash. In Malawi, over 95% of households depending on biomass (e.g. wood, charcoal, crop residues, animal dung) as their main source of fuel.[188] Incomplete combustion using traditional "open-fire" cooking methods produces high levels of pollutants such as CO and PM.[189,190]Exposure to solid fuel use assessed through questionnaires and interviews is associated with increased pneumonia risk in children aged under five years.[191,192] However, the few studies that assessed exposure through objective measurements of CO and $PM_{2.5}$ have not confirmed this association, raising the possibility that this association is at least partly explained by confounding by other poverty-related exposures.[193] Increased respiratory infections in early childhood may lead to long term defects in lung function, as discussed in section 2.3.2.7.

The effect of household air pollution on wheezing and asthma is unclear. ISAAC reported an association between the use of open fires for cooking and increased wheeze (OR 2.17 (95% CI) 1.64-2.87).[194] However, a previously published meta-analysis of four small asthma studies in children exposed to biomass fuels was inconclusive, reporting a pooled OR of 0.5 (95% CI 0.12-1.98).[191] Young children are susceptible to high concentrations of particle deposition in lung tissue, due to physiological and anatomical factors.[195] Environmental exposures, including inhaled pollutants, during critical periods of lung growth and development may lead to irreversible long term deficits in adult lung function.[55,178]

2.3.2.7 *Respiratory infections in early life*

The importance of childhood respiratory infections on mortality in childhood and adult lung function is well recognised.[129,196] Acute respiratory infections are the leading cause of death in children aged under five years worldwide, and may lead to long term sequelae in survivors, particularly in populations with significant comorbidity, such as HIV and malnutrition.[197,198]

A meta-analysis evaluating long-term pneumonia outcomes in children under 5-years, reported the risk of serious sequelae (restrictive lung disease, obstructive lung disease, bronchiectasis) as 13.6% and 5.5%, in hospitalised

and non-hospitalised children respectively, with the highest risk (15.7%) in children from Africa.[199] Minor sequelae (including chronic bronchitis and asthma) were also reported in 6.7% of children overall.

Wheezing illnesses in infancy due to respiratory syncytial virus (RSV) and rhinovirus are associated with increased risk of childhood asthma in later childhood.[200] Adenovirus infection is associated with the highest rates of long-term sequelae, including development of bronchiolitis obliterans in LMIC.[199,201]

Globally, RSV is the commonest cause of childhood respiratory infection, with the highest incidence seen in LIC.[202] Rhinovirus is the most frequent causative agent of upper and lower respiratory tract infections in infants and young children.[203] Rhinovirus and RSV are both common in Malawi; RSV was detected in 12%, and rhinovirus in 20%, of severe acute respiratory illness cases seen in the paediatric department at Queen Elizabeth Central Hospital, Blantyre, between 2011-2014.[204]

Children from a high-risk birth cohort (with parental allergy or asthma) showed an increased risk of asthma at age 6 years, following wheezing viral infections in the first 3-years of life: OR 2.6 with RSV, OR 9.8 with rhinovirus and OR 10.0 with RSV/rhinovirus co-infection.[205] This increased asthma risk persisted at age 13-years following early life rhinovirus infection (OR 3.3 [95% CI: 1.5-7.1]) but not RSV infection.[206] Spirometric assessment of children in this cohort at age 8-years demonstrated significantly decreased lung function; FEV_1 ($p=0.001$) and Forced Expiratory $Flow_{25-75}$ ($p<0.001$), in children with wheezing RV infection in the first 3-years of life.[207] Aeroallergen sensitisation (measured by allergen-specific IgE) led to an increased risk of rhinovirus wheezing throughout the first 6-years of life (RR 2.3, 95% CI: 1.3-4.0).[208]

The Tucson Children's Respiratory Study Group reported an increased prevalence of wheeze (both frequent and infrequent) until age 11, following a relatively mild RSV LRTI (not requiring hospitalisation) during the first 3-years of life.[209] However, by age 13-years this risk was no longer significant. In

contrast, a cohort of children with severe RSV LRTI in the first year of life demonstrated an increased prevalence of allergic asthma and decreased lung function, compared to controls, at age 18-years.[210]

The question remains as to whether respiratory virus infection in early life is a causal factor in the development of asthma, or whether the association represents a vulnerability to viral infections in children with pre-existing airway abnormalities.[203] The DCHS identified LRTI as an independent risk factor for reduced lung function at age 1-year, independent of baseline lung function.[126] There are biologically plausible mechanisms for a causal relationship: inflammatory mediators induced by viral infection in early life may alter adaptive and innate immune responses and lead to remodelling of the developing alveoli and airways.[211] HIV-infected children are at increased risk of infection from common childhood respiratory pathogens (viral and bacterial), and opportunistic pathogens such as *Pneumocystis jirovecii*, cytomegalovirus and *Mycobacterium tuberculosis*.[198] Adolescents from sSA with perinatally acquired HIV infection have high rates of chronic respiratory symptoms, abnormal spirometry and chest radiographic abnormalities with increased burden among those with delayed diagnosis.[212] HIV-exposed uninfected children show altered lung function in early life, with greatest risk for children of mothers with more severe disease.[128]

Both immunocompetent and HIV-infected children are at risk of TB infection in a high prevalence country, such as Malawi. Late diagnosis or inadequate treatment, may lead to long term lung complications, including scarring and bronchiectasis.[213]

2.3.2.8 *Atopic sensitisation and asthma*

Atopic sensitisation and asthma are strongly associated, but it is unclear whether atopy is a causal risk factor for asthma.[200,214] Atopy – the tendency to produce an exaggerated IgE immune response to an environmental exposure – is one of the main risk factors for asthma in high income settings. Allergens reported in African studies of atopy include cockroach, mango blossom and mouse, in addition to common allergens found in HIC; house dust mite, cat,

dog, grass and tree pollens. [74,83] Exposure levels are likely to differ between high- and low-income settings due to lifestyle differences: for example, pets in LMIC are predominantly kept outdoors.[215]

ISAAC Phase 2 reported increased atopic sensitization and asthma symptoms in more affluent countries, and suggested that non-atopic asthma might be more prevalent in LMIC.[214] Of note, only one country from sSA (Ghana) was included in the analysis. Atopic sensitization and allergic diseases are increasing in Africa, along with urbanisation and associated lifestyle changes.[216] Rates of atopic sensitisation have doubled in Ghana over a 10-year period, particularly among children from wealthier urban settings (from 10.6% to 20.2%), with sensitisation to house dust mites (6.4%), cat (4.6%) and dog (3.1%).[79]

Previously reported low rates of asthma in African studies were speculated to be due to intestinal helminth infection, with the hypothesis that parasite-induced non-specific IgE might block receptor sites on mast cells and basophils, and prevent development of atopic disease. However, studies conducted in LMIC over recent decades have produced conflicting results: individual responses to parasite infections are likely to differ depending on the intensity and duration of infection, and helminth species.[217] For example, hookworm infection has been associated with a reduction in asthma (OR 0.50, 95% CI: 0.28-0.90, 9 studies), and *Ascaris lumbricoides* with an increased risk (OR 1.34, 95% CI: 1.05-1.71, 20 studies).[218]

The development of atopy and allergic disorders, such as asthma, eczema and rhinitis, are influenced by a complex interaction of socioeconomic, environmental, dietary, and genetic factors.

There is a strong genetic predisposition to atopy and allergic diseases, which often cluster within families. Genetic predisposition is an important but poorly understood risk factor for childhood asthma.[200] While it is well recognised that a positive family history increases the likelihood of asthma developing in a child, inheritance does not follow a classic Mendelian pattern.

Many genetic loci across many chromosomes have been associated with asthma, with each gene contributing only a small fraction of disease risk, and heterogeneity of clinical phenotypes further confusing attempts to define the disease at a genetic level.[219] To date, there is a lack of published data exploring genetic profiles of asthmatic individuals in sSA.

2.3.2.9 *Exposure to inhaled pollutants in adulthood: tobacco smoke, household air pollution and occupational exposures*

The detrimental effect of active tobacco smoking has been long established, with longitudinal studies documenting accelerated decline in FEV_1 among smokers compared to non-smokers.[220] Active smoking during adolescence impairs lung growth, meaning that lung function in young adults starts to decline from a lower peak FEV_1.[221] Once lung function decline begins, moderate to heavy smoking men have, on average, an annual decline in FEV_1 15ml greater than non-smokers, with a slightly lower effect reported among female smokers.[220]

Accelerated FEV_1 decline is one route by which patients may reach a lung function threshold in keeping with COPD.[222] In those with mild-moderate COPD, smoking cessation has been reported to result in an improvement in FEV_1 (47ml on average) in the year after quitting, and a subsequent reduction in the rate of decline: mean (standard deviation (SD)) 31 (±48) ml/year compared to 62 (±55) ml/year in continuing smokers.[223] However, recent data from six US population based cohorts reported FEV_1 decline at the median age (57 years) of 31.0 ml/year (95% CI: 30.7-31.4) in never smokers, 35.0 ml/year (95% CI: 34.4-35.6) in former smokers and 39.9 ml/year (95% CI: 38.9-40.9) in current smokers, suggesting that the ongoing process of progressive lung damage continues even after smoking cessation.[224] Of particular relevance to sSA, active smokers are at increased risk of TB infection, with potential long-term respiratory sequelae.[225] Compared to high-income settings, the incidence of lung cancer is relatively low in sSA, although data are unreliable due to challenges in diagnosis and reporting; tobacco smoking

is an important risk factor and explains the higher burden of lung cancer reported in men throughout the region.[226]

The effects of household air pollution on adult lung health are likely to be most pronounced among women, due to greater involvement in domestic activities, including daily cooking.[227] Studies have demonstrated increased respiratory symptoms (cough and sputum production), chronic bronchitis and obstructive airways disease among women who cook with biomass fuels.[191,228,229]

The WHO identifies household air pollution, arising from solid fuel use for cooking, as a major risk factor for COPD worldwide.[227] However, the studies informing this conclusion have largely included self-reported biomass fuel use, rather than objective measurement of pollution, and heterogeneous outcome variables, rarely including post-bronchodilator spirometry to diagnose COPD.[230] Recent meta-analyses report conflicting results; a meta-analysis of 25 BOLD study sites found no association between airflow obstruction and self-reported use of solid fuels for cooking or heating, in LMIC and HIC, while a pooled analysis from 13 LMIC sites reported increased COPD in those with self-reported household air pollution exposure (adjusted OR 1.41 [95% CI: 1.18-1.68]).[96,231] The challenges in relying on self-reported exposure data, which is subject to recall bias and misclassification, and inadequate adjustment for confounding factors are potential explanations for the conflicting results; furthermore all included data were from cross-sectional surveys and therefore suboptimal for assessing a causal relationship.

Intervention studies aiming to reduce household air pollution exposure and improve respiratory outcomes for adults have also yielded inconclusive results.[232]

An RCT conducted in Mexico, comparing a Patsari chimney stove intervention with continued use of open fire for cooking, reported a significant reduction in respiratory symptoms and lung function decline among women who adhered to the intervention. Annual decline in FEV_1 was 31ml among Patsari

users, compared to 61ml in those using open fires. However, only half of participants adhered to the intervention, and on intention-to-treat analysis of lung health indicators, no impact was observed.[233]

The RESPIRE study in the Guatemalan highlands randomised women to receive a chimney woodstove (plancha) or continue cooking on a traditional indoor open fire. Women in the intervention arm reported reduced respiratory symptoms, especially wheeze, at follow-up but no significant effects on lung function were observed after 12-18 months.[234] Further analysis reported an association between CO in exhaled breath levels (a proxy for household air pollution exposure), respiratory symptoms and decreased FEV_1.[235] However, lung function was not associated with average post-intervention personal 48-hour CO exposure, measured by passive diffusion tubes at various timepoints.[235] The inconsistent results from the two methods of CO measurement in this study cause more confusion than clarity and highlight the challenges in obtaining accurate measurement of personal exposure to household air pollution.[236]

Although an uncommon diagnosis in Malawi, occupational lung disease is a considerable problem among miners (of gold, platinum and diamonds) in mineral-rich sSA countries.[237] Inhalation of silica dust by South African gold miners causes inflammation and irreversible nodular fibrosis of the lungs known as silicosis with lung function decline proportional to the degree of pulmonary changes.[238] Silica dust exposure and silicosis have additional negative impacts on lung health, as strong risk factors for pulmonary TB.[239,240] The majority of Malawians work in agriculture (59% women, 44% men), usually subsistence farming, or perform unskilled manual labour (20% women, 25% men).[10]

2.3.2.10 *HIV and TB in adulthood*

Despite advances in screening and access to treatment, sSA continues to face the greatest global burden of both HIV and TB infection.[241,242] In sSA in 2017, an estimated 723,000 people were diagnosed with new HIV infection and 712,000 people died from HIV.[241] In 2015-16, the overall HIV prevalence

among those aged 15-49 years in Malawi was 10.4%, with higher rates among women (12.2%) compared to men (8.3%).[10] Many HIV-infected people living in LMIC experience serious or fatal lung complications; impaired host defences increase the frequency and severity of bacterial, mycobacterial, fungal, viral and parasite infections. Additionally, non-infectious lung disorders; lung cancer, pulmonary arterial hypertension and COPD, are more common in HIV-infected individuals.[243] Among those living with HIV/AIDS, TB is the major cause of mortality worldwide.[243] However, although HIV and TB are common co-infections in sSA, worldwide in 2016 the majority of new TB cases and deaths occurred in HIV-negative individuals.[242]

HIV is the most important risk factor for developing active TB in Malawi: the prevalence of TB climbed rapidly in parallel with HIV prevalence, peaking around 2004 when the national scale-up of anti-retroviral treatment (ART) began.[244] Since then, TB cases have started to fall: in 2014 the national TB prevalence survey reported ~18,000 cases compared to ~28,000 in 2003.[245]

TB is associated with considerable morbidity, with increasing recognition of the long-term consequences of infection.[246] Up to half of TB survivors have some form of persistent respiratory dysfunction despite microbiological cure, with a wide range of structural abnormalities and consequent symptoms.[247] Cavitation, bronchiectasis and fibrosis are the main features seen on chest x-ray, with nodules, consolidation and emphysema identified using CT imaging.[248] Resulting lung function impairment may include both obstructive and restrictive patterns, with increasing evidence that TB plays a role in the development of COPD.[247,249]

2.3.2.11 *Emerging threats in sSA*

Research from HIC suggests that obesity increases an individual's risk of developing asthma and may lead to more severe disease and resistance to asthma treatment.[250] Although previously considered a problem of HIC, childhood obesity is now a growing concern across the globe, including LMIC.[251] Childhood obesity rates are generally low in sSA, however southern Africa had the largest proportional rise in obesity among 5- to 19-year olds

between 1975 and 2016, globally.[251] In southern Africa, 13.7% children under 5-years age are overweight, compared to <5% in eastern, middle and west Africa.[252] This increasing public health problem is likely to have a major impact on the prevalence of non-communicable diseases, including chronic respiratory conditions, across sSA. Further research is needed to explore obesity prevention interventions in LMIC, to impact on dietary behaviours and physical activity levels.[252]

Another emerging global public health concern is the use of electronic cigarettes (e-cigarettes), particularly among young people. Lack of long-term safety data means that the effect of chronic exposure to e-cigarette emissions, containing nicotine, volatile carbonyls, reactive oxygen species, furans and metals on respiratory health is unknown.[253] As discussed earlier, *in utero* exposure to nicotine may adversely affect lung development, and maternal e-cigarette use in pregnancy is therefore concerning. At present e-cigarette use is low in sSA; data from the 2016 South African Demographic Health Survey reported the prevalence of e-cigarette use as 2% and 3% in women and men respectively, compared to cigarette smoking rates of 7% and 36%.

The global impact of the COVID-19 pandemic has highlighted the fragility of overstretched health care systems, particularly in LMIC where even basic medical supplies and equipment are lacking. The long-term respiratory effects of novel pathogens, such as coronavirus SARS-CoV-2, are unknown. Longitudinal study of cohorts of infected individuals from diverse populations across the world, with differing co-existing risk factors, would be helpful here.[254]

Having explored the literature relating to the epidemiology of NCD-L in sSA, and potential factors influencing lung health across the life course, I will now focus on the clinical management of asthma. The remaining sections will review literature of particular relevance to the studies comprising chapter 5 and 6 of the thesis, and focus on monitoring asthma control (symptoms, airflow abnormalities and inflammation) and the treatment of asthma in LIC, including challenges and potential solutions.

2.4 Asthma: clinical assessment of a heterogenous condition

It is well recognised that asthma is a heterogeneous condition, and that the symptoms associated with asthma, can arise from a variety of underlying pathophysiology.[36] Several phenotypes have been described including; allergic asthma, non-allergic asthma, late-onset asthma, asthma with fixed airflow limitation and asthma with obesity.[44] Importantly, airway abnormalities which accompany the characteristic symptoms; airflow limitation, airway hyperresponsiveness and airway inflammation, are present in varying degrees, and in some cases may be absent.

2.4.1 Monitoring asthma control

Asthma control has two components; evaluation of current symptoms and future risk. GINA recommends the use of four questions to assess asthma symptoms over the previous four weeks and categorise patients into three levels of asthma control – see Table 2-5. There are a number of other questionnaires which have been developed to monitor asthma control; the Asthma Control Test (ACT) and Asthma Control Questionnaire are the most extensively validated.[255] The ACT comprises five questions, giving a composite score ranging from 5-25.[256] The ACT has been used in Nigeria, with 106 adult patients, and found to be an objective and reliable tool for determining asthma control, correlating with percentage predicted FEV_1 and quality of life measures. In this study, 43% had good control (ACT ≥20), 32% poor control (ACT 16-19) and 25% very poor control (ACT ≤14).[257] In Uganda, responses to the ACT and GINA assessment tool were similar; the ACT identified 17%

participants with good control, 43% with poor control and 40% with very poor control.[258]

Table 2-5. GINA assessment of asthma symptom control

In the past 4 weeks, has the patient had:	Level of control
Daytime asthma symptoms more than twice/week? Any night waking due to asthma? Reliever needed for symptoms more than twice/week? Any activity limitation due to asthma?	None: well controlled 1-2: partly controlled 3-4: uncontrolled

The Childhood ACT (cACT) has been developed for use with children aged 4-11 years and includes seven questions; four answered by the child and three by their parent, giving a composite score ranging from 0-27.[259,260] The questionnaire has been translated and validated in several languages, and used, although not validated, in South Africa.[261-263] The mean (SD) cACT score was 19.86 (4.49) for 59 paediatric patients attending a tertiary hospital asthma clinic in Johannesburg, South Africa.[263]

The minimal clinically important difference has been defined as 3-points for the ACT, although this has not been established for the cACT.[264]

2.4.2 Measuring airflow limitation

Asthma is characterised by variable expiratory airflow limitation, which can be measured objectively using spirometry. The variable nature of the condition means that the lung function of an affected individual can vary between completely normal and severely obstructed, depending on intrinsic and extrinsic factors. Within-day variability is greatest in patients with poor asthma control, whereas during acute exacerbations airflow obstruction increases steeply and response to bronchodilators may be impaired.[265]

FEV_1 is reported to predict subsequent asthma exacerbations in children: a percentage predicted FEV_1 of <60% is associated with an OR 2.1 (95% CI: 1.3-3.4) for an attack in the following year, and FEV_1 60-80% OR 1.4 (95% CI: 1.2-1.6).[266] However, FEV_1 percent predicted does not differ with asthma severity

(measured by symptom frequency and medication use) and many children with poorly controlled asthma have normal lung function in between exacerbations.[267] FEV_1/FVC appears to correlate more closely with symptoms, decreasing with increasing asthma severity.[267] However, it is also recognised that patients with chronic airway obstruction, as opposed to an acute episode of wheeze, may have decreased perception of their symptoms.[268]

Bronchodilator response is considered a key feature of asthma; defined for children as an increase in FEV_1 of >12% predicted value, 10-15 minutes after bronchodilator administration.[44] However, bronchodilator response discriminates poorly between asthmatic and healthy individuals and shows considerable within-subject variability; many asthmatic patients will have bronchodilator response values within the normal range.[269]

Airway obstruction and hyperresponsiveness improve on inhaled corticosteroid (ICS) treatment, with the greatest benefits seen in the first 3-months of treatment.[270]

2.4.3 Measuring airway hyperresponsiveness

Airway hyperresponsiveness or bronchial hyperreactivity is another aspect of asthma, which can be measured objectively using direct (inhaled histamine or methacholine) or indirect (exercise, mannitol, hyperosmolar saline) tests.[271] During an exercise test there is a transient dehydration of the airway surface, which causes the release of mediators (e.g. prostaglandins, leukotrienes and histamine) and subsequent contraction of airway smooth muscle.

Standard protocols for exercise challenge tests involve a sustained effort for 6-minutes, with sufficient intensity to raise the heart rate to a target value within the first 2-3 minutes of exercise.[272] The American Thoracic Society defines exercise induced bronchoconstriction (EIB) as a ≥10% fall in FEV_1 from the baseline value, measured within 30 minutes after exercise, but comments that studies in children have recommended a higher threshold of ≥15%.[273] GINA guidelines define a positive exercise challenge test in children as a fall in FEV_1 of >12% predicted, or PEF>15%.[44] However, the literature contains a

variety of exercise test protocols, summarised in Table 2-6 which makes direct comparison of results difficult.

Table 2-6. Variation in exercise challenge test protocols.

	Measure of lung function	*Timing*	*Threshold for a positive test*
Haby 1994[274] Australia	FEV_1: 2 within 100ml	3,5,10 mins	13%
Haby 1995[275] Australia	FEV_1: 2 within 100ml	3,5,10 mins	15%
Powell 1996[276] UK	PEFR: best of 3 attempts	5,10,15 mins	15% or 20%
Addo-Yobo 2007[79] Ghana	PEFR: best of 3 attempts	5,8 mins	12.5%
Mashalane 2006[78] South Africa	PEFR: best of 3 attempts	3,10 mins	10% or 15%
Terblanche 1990[85] South Africa	FEV_1: 2 within 5%	10-15 mins	10%
Ng'ang'a 1998[277] Kenya	FEV_1: best of 3, within 100ml	5,10 mins	15%
Perzanowski 2002[73] Kenya	FEV_1: best of 3 reproducible	5,10 mins	15%

Although airway hyperresponsiveness is a recognized airway abnormality among asthmatics, it may not be detectable in a significant proportion of patients.[49] Airway hyperresponsiveness may also be present in individuals without a known diagnosis of asthma.[273] Hence, although the detection of airway hyperresponsiveness may contribute to clinical assessment, it is no longer considered an essential screening tool in epidemiological studies.[46]

2.4.4 Assessing airway inflammation

The pathophysiology of school age asthma in HIC is well understood: there is a background of respiratory allergy with type-2 T-helper cell mediated eosinophilic inflammation of the lower airways and reversible airflow obstruction. Mast cells and antigen-specific type-2 T-helper cells produce cytokines, and interleukin-4, interleukin-5 and interleukin-13.[278] An additional insult such as a viral or bacterial infection, or a sudden increase in allergen exposure results in an acute attack, with a rapid, marked increase in airway obstruction.[279]

However, allergic asthma may account for only half of asthma cases, with non-eosinophilic cases showing a picture of neutrophilic, mixed granulocytic (raised eosinophils and neutrophils) or paucigranulocytic (normal levels of eosinophils and neutrophils) airway inflammation.[280-282] Among a birth cohort of UK children, similar proportions (~10%) were classified as having atopic and non-atopic wheeze at age 10 years.[283] Among a cohort of Brazilian children, 70% of asthmatics were nonatopic, defined by negative skin prick tests to a panel of six relevant aeroallergens.[284] A subsample of this cohort underwent sputum induction: neutrophilic inflammation was reported as the predominant feature in sputum from the non-atopic asthmatic children.[285] Non-allergenic exposures including viral infections, bacterial endotoxins, particulate air pollution and ozone are potential contributors to neutrophilic airway inflammation.[281] Features of airway remodelling, including epithelial loss, basement membrane thickening, increase in smooth muscle and blood vessel proliferation have been reported in children with both eosinophilic and non-eosinophilic asthma.[286]

In adults, non-eosinophilic asthma is associated with a poor response to inhaled corticosteroid treatment.[287,288] Information on airway inflammatory phenotype may therefore be useful in guiding treatment and predicting response.

2.4.4.1 *Sputum eosinophilia as a biomarker of airway inflammation*

Analysis of induced sputum from asthmatic children has demonstrated that atopic asthma and eosinophilic airway inflammation are associated with uncontrolled disease.[284,289,290] In a Brazilian cohort, atopic children (defined by one or more positive skin prick tests) with current asthma were more likely to have ≥4 attacks during the previous year (OR 2.6, 95% CI: 1.04-6.4)[284] Children classified as having eosinophilic asthma (with sputum eosinophils >2.5%) had increased symptoms and bronchodilator use during a 5-year follow-up period.[290] A study of 146 asthmatic children found sputum eosinophilia was significantly associated with frequency of symptomatic episodes in the

previous 12-months, although the relationship with current symptoms (in past 2-weeks) and lung function was less strong.[289]

The studies mentioned above collected sputum at only one time point: however longitudinal analysis including 59 children with mild, moderate and severe asthma demonstrated that sputum inflammatory phenotypes are not stable over time.[291] Over a 6-12-month follow-up period, 63% of children demonstrated two or more phenotypes, with phenotype variability unrelated to asthma severity, symptom control or change in inhaled corticosteroid treatment.[291] Only one paediatric study has explored using sputum eosinophils to adjust asthma medication: sputum was collected 3-monthly from 55 children with severe asthma and treatment altered according to either a conventional symptom-based strategy or an inflammation-based strategy (guided by sputum eosinophils).[292] Exacerbation rates and daily symptoms were lower in the inflammatory management group, but not at a significant level. Increasing the frequency of sputum assessment may have yielded improved control, but this would likely be unacceptable to a paediatric population.

2.4.4.2 *Exhaled nitric oxide (FeNO) as a biomarker of airway inflammation*

In the lungs, nitric oxide gas (NO) is produced by two enzymes: constitutive nitric oxide synthetase, which continually generates low concentrations of NO in response to physiological stimuli, and inducible nitric oxide synthetase, which is influenced by various inflammatory cytokines, particularly interleukin-4 and interleukin-13.[293] Exhaled nitric oxide (FeNO) is therefore thought to directly reflect type-2 T-helper cell-mediated inflammation, characteristic of allergic asthma, and has been explored as an attractive non-invasive clinical tool to guide asthma diagnosis and treatment.[294]

According to American Thoracic Society guidelines, a symptomatic, ICS naïve child with a FeNO <20 parts per billion (ppb) is unlikely to have eosinophilic airway inflammation and an alternative diagnosis should be explored; in contrast, a similar child with a FeNO level >35ppb is likely to have significant eosinophilic airway inflammation, and should respond well to ICS.[295]

The use of FeNO in guiding titration of ICS therapy has been evaluated in a meta-analysis of eight paediatric RCTs: children whose treatment was adjusted according to FeNO experienced significantly fewer exacerbations (OR 0.58, 95% CI: 0.45-0.76), although there was no difference in symptom scores or quality of life measures.[296] The largest multi-centre RCT included in the meta-analysis recruited 546 asthmatic patients in the USA, aged 12-20 years. The mean number of days with asthma symptoms did not differ between the FeNO monitoring group and the control group (difference 0.04 days, 95% CI: -0.22 - 0.29), despite receiving significantly higher doses of ICS.[297] The authors of the meta-analysis reported several limitations, including heterogeneity between studies relating to definition of exacerbation, cut-off levels for FeNO, and adjustment of medication.[296] At present there is insufficient evidence to support the use of FeNO to guide treatment in routine clinical practice, although measurement may be beneficial in patients with frequent exacerbations.[296]

FeNO may be useful in predicting loss of asthma control during ICS treatment reduction or cessation, however the evidence to date is limited.[293] One small study monitoring FeNO levels in children after withdrawal of steroid treatment, reported that raised levels 2-4 weeks were seen in children who relapsed (n=9), although more children with raised FeNO did not relapse.[298] Another small study (n=40) monitored FeNO during a period of ICS reduction: exhaled FeNO ≥22 ppb was a significant predictor of failed treatment reduction, although FeNO as a continuous variable was not.[299] Retrospective analysis found that excluding children with FeNO≥22 ppb from ICS reduction could have prevented an exacerbation in 11/14 (78%) children; conversely 19/49 (39%) of children would have continued on ICS, when reduction would have been successful.

2.5 Long term management of asthma: challenges in LMIC

The goals of asthma management are to achieve good symptom control and to minimize the risk of exacerbations, permanent lung damage and treatment side-effects.[44]

2.5.1 Treatment guidelines for LMIC

Treatment guidelines for LMIC are extrapolated from resource-rich settings, and advise a stepwise approach to asthma management; starting with inhaled short-acting β_2-agonist (SABA), with the addition of regular ICS (e.g. Beclometasone), at escalating doses, if symptoms occur frequently – see Figure 2-3. However, these LMIC guidelines contrast greatly from the increasingly complex approach to asthma management now advocated in HIC, focusing on a personalised approach, considering individual risk factors, comorbidities and asthma phenotype. GINA recommends that all adolescents and adults, even those with mild asthma, should receive ICS, and there are a variety of inhalers combining short- or long-acting β_2 agonists with ICS. Phenotypic investigation is advised for patients with severe asthma in HIC, to assess the appropriateness of add-on treatments such as; tiotropium, anti-IgE, anti-IL5, anti-IL5R or anti-IL4R.[44]

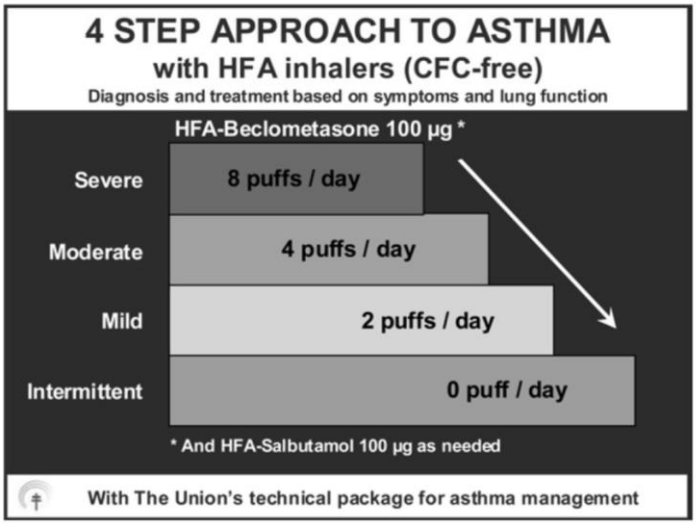

Figure 2-3. The "4-step approach".

From Management of Asthma, IUATLD 2008[300]

For children: HFA-Beclometasone 100µg daily dose; mild: 1 puff, moderate: 2 puffs, severe: 4 puffs

Inhaled medication, from a pressurised metered dose inhaler (MDI) is best given using a spacer device; this is essential to optimise drug delivery. The spacer holds the suspended aerosol after MDI actuation, thus addressing the

difficulty of coordinating simultaneous MDI actuation and inhalation – a particular challenge in children and also during acute attacks.[301] Research from South Africa has shown that a well-constructed "home-made" 500ml plastic bottle spacer is as effective as a conventional, commercially produced spacer for delivery of SABA via MDI for children with acute asthma.[302] In children below 3 years of age, a bottle spacer can be used effectively with the addition of a flexible, well-fitting face mask.[303] In order to be effective, home-made spacers must be constructed and used correctly, and patients and families must understand how to do this.[304,305]

Guidelines for asthma management in LMIC were first published in 1996 by the International Union Against Tuberculosis and Lung Disease – the most "current" version of these are over a decade old.[300] The implementation of these guidelines has been evaluated in several LMICs; Algeria, Guinea, Ivory Coast, Kenya, Mali, Morocco, Syria, Turkey and Vietnam. These clinics were based in urban areas, with oversight by specialist lung physicians, and hence of limited generalisability. Practitioners underutilised PEF measurements to aid asthma diagnosis, underestimated disease severity and under prescribed inhaled steroids, recommended in steps 1-3 of the guideline.[306]

Treatment outcomes, assessed after one year, for a total of 310 asthma patients from seven of these clinics, found that one-third of patients were successfully treated, but suffered from a high rate (37%) of defaulters.[307] In those who adhered to treatment (n=167), asthma severity decreased for the majority of patients, with decreased emergency attendances and hospitalisation.[308] The main challenge identified in these clinics, was adherence to treatment, with the availability of affordable treatment a major obstacle.

2.5.2 Health care systems for chronic disease management

Inhaled medication is the cornerstone of chronic respiratory disease management and recommended in global treatment guidelines for asthma and COPD. The WHO Essential Medicines List includes beclometasone and salbutamol inhalers, yet these medicines are often unavailable, unaffordable

or of unreliable quality in LMICs.[19] In Malawi, salbutamol inhalers are often available at primary health centres, although staff may lack confidence to prescribe inhaled medication, particularly for children, preferring to give oral salbutamol and prednisolone instead. Beclometasone is usually only available at tertiary facilities; however, stock levels are unpredictable, and most families cannot afford to buy inhalers from private pharmacies.

Chronic disease management requires more than medication alone; health care facilities require appropriate infrastructure, diagnostic tools, trained healthcare personnel and appropriate treatment guidelines and referral pathways.[43] Information systems are also crucial to inform policy and planning, and engage government stakeholders.[309]

2.5.3 Asthma awareness; patients, health care providers and communities

A further barrier to treatment adherence is knowledge and understanding of asthma among patients, their families and the wider community. Adverse beliefs and suspicion regarding treatments, particularly inhaled medication, will lead to poor compliance and treatment failure.

In Zambia, one third of participants surveyed believed that inhalers were addictive, and that tablets were a superior asthma treatment to inhalers. Furthermore, there was poor understanding that asthma symptoms can be managed with long-term treatment; only one third believed that hospitalizations were preventable and just over half thought that asthma symptoms are preventable with the correct medication.[310]

Concerns regarding inhaled treatment were also reported from a cross-sectional survey of carers of asthmatic children at a teaching and referral hospital in Kenya.[311] Two-thirds of carers believed that inhalers were only for the very sick, a similar number preferred oral medication (syrups) over inhalers, and only one-third felt that preventer medications were necessary.

A cross-sectional survey of asthmatic adults and children in South Africa, reported that one-quarter were experiencing daily symptoms, and that patients had considerable concerns about their inhaled medication.[312] Almost

one-half of patients were worried about the side-effects and a similar number reported stopping their inhaled medication when they feel well. The authors concluded that under-treatment, inappropriate treatment and lack of patient education are all factors contributing to poor symptom control, and that education of patients and doctors should be prioritised.

2.5.4 Asthma education interventions: patients and families

Good patient education is key to empowering families to take an active role in long-term disease management. *Empowerment of people and communities* is one of the key approaches advocated by the WHO in addressing the global burden of NCDs.[3]

Evidence from RCTs performed in high-income countries, suggests that educational interventions have a beneficial effect on a variety of asthma outcomes. A Cochrane review of 38 trials found that asthma education targeted at families presenting for emergency asthma care resulted in a reduced risk of subsequent emergency visits (RR 0.73, 95% CI: 0.65-0.81) and hospital admissions (RR 0.79, 95% CI: 0.69-0.92) compared to controls.[313] An earlier systematic review of 32 trials, also including children without an emergency attendance in the past year, reported decreased emergency department visits, improved lung function, and reduced school absence and restriction of activities, although no effect on symptom scores.[314] Meta-analysis of asthma education interventions conducted in the USA only (37 trials), found similar positive results, with decreased hospitalisation and emergency department visits in the intervention groups.[315]

The majority of the RCTs included in these reviews were conducted in HIC: there were 2 trials reported from India.[316,317] One RCT assessed the efficacy of an individualised written home management plan for children with moderate persistent asthma, reporting fewer exacerbations, decreased school absence, lower symptom scores and less nocturnal awakening in those children who received a written plan.[317] Another RCT from an outpatient clinic in India, including asthmatic patients aged 10-45 years, reported a reduction in

hospital use following four group sessions relating to self-management of asthma.[316]

The trials included in the three systematic reviews included a wide variety of educational interventions; targeting children, parents or both; with single or multiple sessions of varying durations; delivered to individual participants or in groups.[313-315] It is therefore unclear which are the most important elements of an educational package, in achieving key treatment goals. The studies from the USA suggested that interventions comprising more sessions and with a more interactive format produced better outcomes.[315]

Evidence from studies conducted in adults with asthma has shown that self-management education reduces hospitalisation, emergency visits, days off work or school , night-time symptoms and quality of life.[318] Key features of the educational interventions included self-monitoring (by either PEF or symptoms), in addition to regular medical review and a written action plan. Further analysis, exploring the key components of a written action plan found that the most effective plans were individualised, included 2-4 action points, and detailed how to adjust oral and inhaled corticosteroid treatment.[319]

All the asthma education interventions cited previously were delivered by trained health personnel; nurses, health educators and social workers. There are limited studies reporting the outcomes of asthma education delivered by lay people, with none from LMIC. A small number of studies from high-income settings (USA, Australia and Jordan) have evaluated peer- and lay-led complex asthma interventions for adolescents, suggesting a small improvement in asthma-related quality of life, although the effect on asthma control, exacerbations and adherence are unclear.[320,321] In the UK, self-management education delivered to adults with asthma by trained lay people, resulted in comparable clinical outcomes to patients seen by primary care based practice nurses, with similar associated costs.[322,323] Qualitative exploration of the experiences of these lay educators highlighted the need for comprehensive support and monitoring, particularly at the start of the programme, and the

importance of training, with consideration of content, intensity, and interactive teaching methods, such as role play.[324]

Among inpatients in the USA, asthma education delivered by trained lay volunteers to families of inner-city children with asthma, during an acute hospital admission, was associated with improved asthma management behaviours.[325]

Asthma education is included in international guidelines as an essential component of asthma management, however it is recognised that limited time and resources may affect its delivery.[44,326]

2.5.5 Asthma education: health care professionals

The provision of good quality asthma education for patients and their families also requires that health workers are up-to-date and knowledgeable about both acute and long-term asthma management.

A survey of paediatric clinicians from teaching hospitals in Nigeria found that despite familiarity with GINA guidelines, physicians frequently failed provide a self-management plan or check inhaler technique, as recommended.[327] Similarly, an audit of asthma guideline implementation in primary care facilities in South Africa found that asthma control was poor, despite reasonable availability of inhaled medications. Assessment of current symptom control, review of inhaler technique and provision of a self-management plan occurred in only one in ten asthma consultations.[328] The provision of educational programmes for health care professionals and the public are necessary to combat cultural misconceptions around asthma care, and to ensure widely accessible diagnosis and treatment.[329]

Health workers in Malawi have described a need for training regarding chronic respiratory diseases such as asthma and COPD, particularly amongst primary health centre staff.[330]

2.5.6 Community awareness of chronic respiratory disease

More broadly, community-wide, health promotion strategies are essential to address the growing rates of all NCDs in Malawi.[15] Community education regarding the risks of exposure to indoor air pollution and tobacco smoke plays a key part in the prevention of chronic respiratory conditions. The use of highly polluting biomass fuels for energy requirements including cooking, lighting and heating is widespread in Malawi.[188] Tobacco smoking rates are relatively low (~12%), however there are challenges in delivering anti-smoking public health policies in a country which is heavily reliant on the tobacco industry for domestic revenue.[10,15]

Wider community understanding of chronic respiratory conditions may improve health seeking behaviour, encouraging early presentation and subsequent disease management, although there are many additional factors which affect access to healthcare.[330] A recent cross-sectional survey in rural Malawi found that 23% of adults had chronic respiratory symptoms (cough, wheeze, shortness of breath); of these 88% had sought medical care but only 5% had an appropriate diagnosis (TB, asthma, bronchitis or COPD) recorded in their patient-held medical records.[331] That chronic respiratory conditions are diagnosed at such low rates, suggests a concerning lack of knowledge among health care staff.

2.6 Human resource constraints in Malawi

There is a global shortage of trained medical staff, but this deficit is most catastrophic in the poorest parts of the world where the mismatch between the healthcare need and available resources is greatest: the WHO African Region bears 24% of the global burden of disease, to be addressed with only 3% of health workers and 1% of world health expediture.[9]

Malawi suffers from a shortage of trained clinical staff with 2 physicians and 28 nurses per 100,000 population, well below the WHO recommended ratio of 2.5 health professionals per 1000 population.[8] Currently, there are three tertiary level referral hospitals (Blantyre, Lilongwe and Zomba), 27 secondary

level district hospitals, and 460 primary health care centres.[10] Most patients with NCDs are managed in one of the tertiary care facilities, although there is growing interest in decentralising care, with management of common conditions at the primary health care level.[11] However, appropriate diagnostic testing (spirometry) and long term treatments (inhaler therapy) for chronic respiratory conditions, are not available at district or primary care level facilities.[331]

A survey of Malawi Ministry of Health personnel reported a lack of resources for NCD services including inadequate staff, equipment and supplies.[332] Furthermore, within the country there is a maldistribution of medical staff, with the staffing crisis particularly affecting the rural areas, where 80% of the population reside. The shortfall is addressed by the appointment of mid-level cadres; Clinical Officers and Medical Assistants, who complete a shorter duration of training than physicians completing a 5-year MBBS degree course.[333] Medical Assistants complete a 2-year *Certificate in Clinical Medicine*, with a focus on primary care at the community level, while Clinical Officers complete a 4-year *Diploma in Clinical Medicine*, which includes surgical training. Medical Assistants staff primary health centres and Clinical Officers largely work in the district hospitals.

Efforts to increase the number of health professionals in Malawi must keep pace with staff losses from the health sector. International migration or "brain drain" of doctors and nurses seeking opportunity for improved training, remuneration, working conditions or lifestyle is a constant challenge to the system.[334] Furthermore, mid-level cadres may consider leaving their posts for an alternative career pathway as a result of demotivating experiences; particularly if staff feel undervalued, unfairly treated or unable to provide adequate patient care.[335]

2.6.1 The potential for task shifting

One possible strategy to address the huge shortfall of trained medical staff in LIC is task shifting: "the transfer of a task normally performed by a more highly trained health care worker to another with a different, usually lower

level of training." [336] Tasks can also be transferred to non-medical staff, such as lay health workers, who have received training to perform tasks normally performed by health professionals with more education and higher qualifications.[337]

Task shifting has been widely adopted in sSA in response to the HIV epidemic. A large RCT in South Africa reported comparable clinical outcomes of ART, whether care was monitored by an appropriately trained nurse or a doctor.[338] Several countries in sSA have reported improved quality of HIV care, by adopting a task-shifting approach.[338-340] In Malawi, improved access to HIV services has been achieved through decentralisation of care to primary health centres and community sites, with task shifting of HIV testing and counselling and ART initiation and monitoring.[341] Non-physician clinicians (clinical officers and medical assistants) and nurses are able to initiate ART, following a training course and short clinical attachment at an experienced ART site. Task shifting of HIV testing and counselling, from nurses to trained Health Surveillance Assistants (HSAs) has also been successfully employed. This approach is advocated by the WHO, to promote accessible, equitable and good quality health care for the rapidly expanding number of people living with HIV/ AIDS, who are now taking ART.[336] Improved ART outcomes have also been reported where support has been provided by specifically trained community volunteers in rural Malawi.[342]

Within Malawi, HSAs represent a health provider cadre that could potentially be rapidly expanded to address specific tasks within the health care system. HSAs are community health workers (or lay health workers), who have completed the Malawi School Certificate of Education and 12-weeks of pre-service training. HSAs form 30% of the health workforce in Malawi and are largely responsible for delivering the Ministry of Health Essential Health Package, including the community case management of childhood illness. HSAs are considered the bridge between local communities and the health sector: the strength of these relationships relies heavily on mutual respect and trust.[343] The initial role of HSAs focused on disease surveillance,

prevention and environmental health activities.[344] However, over time the HSA role has extended to involve curative disease management, including maternal and newborn health tasks, such as prenatal care, postnatal care and neonatal assessment.[337] Important considerations when extending the role of HSAs are: ensuring adequate remuneration and opportunities for career progression, strengthening training and supervision, monitoring and prioritising workload, providing adequate resources.[345] Furthermore, community-based disease prevention work will suffer if HSAs spend time filling staffing gaps in health clinics, performing extended tasks such as microscopy, drug management, under-fives clinics and HIV testing and counselling.[344]

Given the success of task-shifting for a broad range of health care services in LMICs, the approach has been suggested as a potential strategy for the management of NCDs.[339] However, there is limited quality research to assess this approach to NCD management; a systematic review of 22 studies (including 2 studies relating to asthma) reported successful task shifting for a variety of non-communicable diseases by non-physician health professionals (nurses, midwives, health workers).[346] Asthma care was provided as part of a nurse-led primary-care intervention for multiple NCDs in rural South Africa: the authors reported improved treatment adherence, with asthma control achieved in 84% of patients using standardised treatment and referral protocols.[347] A study from rural Cameroon reported decreased exacerbations over a median follow-up period of 5 months for patients attending nurse-led asthma clinics, although 41% were lost to follow-up.[348] In Kenya, a programme has been successfully introduced, with nurse-led management of multiple NCDs (hypertension, type 2 diabetes, epilepsy, asthma and sickle cell disease) according to clinical protocols.[349] Successful implementation of such task-shifting programmes require appropriate training programmes, access to standardised protocols, and supply of relevant equipment and medication.[346] Task shifting may present a potential solution to improve NCD management in Malawi, but further disease-specific research is needed to assess feasibility,

acceptability to health care workers, patients and their families, and clinical outcomes.

2.7 Summary

There is a lack of data relating to NCD-L in sSA, particularly for children and those living in rural areas. Limited data suggests that asthma and COPD are increasingly common, and that asthma symptoms may be poorly controlled in low-income settings. Uncontrolled disease may relate to lack of community and health provider awareness, and challenges with diagnosis, long-term monitoring, and availability and understanding of treatment, compounded by poorly equipped health care facilities with severe shortages of medical staff. Factors which may have an adverse effect on lung health can act at various points in the life course (*in utero*, during childhood, adolescence and adulthood). Potential risk factors for poor lung health are frequently encountered in LIC, such as Malawi; adverse antenatal environments lead to *in-utero* growth restriction and prematurity; HIV and respiratory infections, including TB are common; exposure to air pollution is widespread, including household air pollution from biomass fuel use.

The original research presented in the following chapters attempts to address some of the existing gaps relating to NCD-L epidemiology in Malawi and explore task-shifting as an approach to improve asthma management in a resource-limited setting.

3 Lung health and exposure to air pollution in Malawian children: a cross-sectional study

3.1 Introduction

Non-communicable lung diseases are major global health priorities across the life course.[20,53] Asthma is the commonest chronic disease of childhood and one of the commonest chronic diseases of adulthood, affecting around 358 million people whilst COPD affects 174 million people, worldwide.[17]

Although most of the children and adults with these conditions live and die in low- and middle-income countries (LMICs), the majority of the research into these conditions is done in high-income countries. Research is especially scarce in the LMICs of sub-Saharan Africa where limited studies suggest the prevalence of childhood asthma is increasing in urban settings, and that children with symptoms of asthma are likely to be severely symptomatic. [51,67] In adult populations, Burden of Obstructive Lung Diseases (BOLD) studies from countries in sub-Saharan Africa, including sites in urban and rural Malawi, have found a high burden of impaired lung function – particularly low Forced Vital Capacity (FVC)[22,64,90] – which is concerning given the association between low FVC and mortality in other populations.[24]

In these same sub-Saharan African populations, there is widespread reliance (by around 700 million people) on inefficiently burned solid fuels for cooking, heating and lighting.[350] Studies in rural Malawi report exclusive biomass fuel use (wood, crop waste and charcoal) with households using traditional "open-fire" cooking methods.[26] The widespread exposure of children to pollutants such carbon monoxide (CO) and particulate matter, resulting from incomplete fuel combustion, is particularly concerning. Household air pollution has been suggested as a potential contributing factor in the development of non-communicable lung diseases in low-income countries.[190] However, the links between household air pollution exposure, new-onset asthma in children and obstructive lung disease in adults, are unclear, with controversy over the

interpretation of available data.[96,191,194,230,231] Environmental exposures, including inhaled pollutants, during periods of lung growth and development may lead to irreversible long term deficits in adult lung function.[55,178]

In this context, the Cooking and Pneumonia Study (CAPS) was done to determine whether an intervention comprising two cleaner burning biomass-fuelled cookstoves and a solar charger would reduce the incidence of Integrated Management of Childhood Illness (IMCI)-defined pneumonia in children under the age of 5 years in rural Malawi compared to continuation of traditional cooking methods.[26] CAPS recruited households from village clusters in Chikhwawa between December 2013 and February 2016. The primary intention-to-treat analysis found no difference in pneumonia incidence between the two trial arms. Recently reported secondary analyses in adults from a sub-set of CAPS households found no difference in chronic respiratory symptoms, lung function or personal air pollution exposures between participants from the intervention and control groups.[23] That said, median exposure to fine particulate matter ($PM_{2.5}$) was 71 $\mu g/m^3$, well above WHO annual and 24-hour guidelines.

Is it not known whether the same pattern of respiratory symptoms, spirometric abnormalities and air pollution exposures would be seen in children as in adults or whether the CAPS intervention would have beneficial effects on any of these outcomes in children. In this paper we report the findings of a cross-sectional study, conducted in the same village communities as CAPS, which set out to: 1) measure the prevalence and determinants (including measured exposure to household air pollution) of non-communicable lung disease in a population representative sample of children in rural Malawi and 2) conduct an analysis comparing lung function between young children in the intervention group and those in the control group in CAPS.

3.2 Methods

3.2.1 Study design

We conducted a cross-sectional study of the prevalence and determinants of non-communicable respiratory disease among children living in Chikhwawa District, Malawi.

3.2.2 Setting

Chikhwawa is a rural area, located in the Southern Region of Malawi on the Shire River, 50 kilometres from the nearest city, Blantyre. The population consists largely of subsistence farmers living in village communities and is highly vulnerable to climatic shocks, having experienced flooding, crop failures, and famine in recent years. Infectious diseases (malaria, pneumonia and gastroenteritis), HIV/AIDS, malnutrition, and limited access to basic healthcare contribute to high childhood mortality rates, although a considerable reduction in the mortality rate for children under 5 years old has been seen in Malawi over the past 25 years.[42]

3.2.3 Participants

Following widespread community engagement events, children aged between 6 and 8 years, living in households that had taken part in CAPS and BOLD-Chikhwawa were identified by local community advisors and invited to participate if the child's parent/guardian gave written informed consent (or witnessed thumbprint for those unable to read and write). Verbal assent was sought from the children. Exclusion criteria were current treatment for tuberculosis, current acute respiratory infection (defined as cough of <1-week duration, associated with fever and/or increased work of breathing) and other contraindications to spirometry (chest or abdominal pain, haemoptysis). We recruited all children from the study area meeting the eligibility criteria.

3.2.4 Procedures

Fieldworkers visited the children in the community to administer an electronic questionnaire, and assess anthropometry, lung function, and personal exposure to household air pollution. An electronic questionnaire was

administered in Chichewa, the local language; parents answered questions detailing respiratory symptoms and potential contributing factors. Core written questions from the International Study of Asthma and Allergy in Children (ISAAC) were included, which had been forward and back-translated.[52] Height, weight and mid-upper arm circumference (MUAC) were measured according to standardised protocols. Height and weight were interpreted using the WHO 2007 child growth standards.[351] MUAC was used to assess nutritional status.[352]

Pre and post-bronchodilator spirometry was performed by BOLD centre-certified technicians, according to American Thoracic Society/European Respiratory Society (ATS/ERS) standards using an Easy On-PC Spirometer (ndd Medical Technologies; Zurich, Switzerland).[58] Regular calibration was performed according to the manufacturer's instructions. The highest Forced Expiratory Volume in 1 s (FEV_1) and FVC measurements for each participant were selected (from a maximum eight attempts), before and after administration of 400 µg inhaled salbutamol, via Volumatic spacer. Reversibility was defined as ≥12% improvement between pre- and post-bronchodilator FEV_1.

Spirometry overreading was performed by two independent reviewers. Two sets of ATS/ERS standards (aged 4-6 years and aged 7 and above) are relevant for the children in this study.[58,353] As the age range of our study children overlaps both sets of standards, and to maximise the use of spirometric data collected, we defined acceptable (grade C) quality as two traces within 150 ml or 10% (Table 3-1).

Table 3-1. Quality grading for spirometry

Quality grade	**FEV_1 or FVC**
A	3 acceptable trials within 5% or 100ml
B	2 acceptable trials within 5% or 100ml
C	2 acceptable trials within 10% or 150ml
D	One acceptable trial
F	No acceptable trials

Carboxyhaemoglobin level (COHb) was measured at a single time-point using a Rad-57 pulse CO-oximeter (Masimo Corporation, California, USA). Performance verification was ensured at study outset, according to the manufacturer service manual. To assess personal carbon monoxide (CO) exposure levels, children wore an EasyLog CO USB data logger (Lascar Electronics Ltd., Wiltshire, UK), for up to 48 hours, starting immediately after the field visit.

3.2.5 Variables

Clinical outcomes were presence or absence of symptoms, as assessed by the following questions; *Chronic cough*: defined by a positive response to both "Does your child usually have a cough when they don't have a cold?" and "Are there months in which they cough on most days?"; *Current wheeze*: "Has your child had wheezing or whistling in the chest in the past 12-months?"; *Severe asthma:* current wheeze, and ≥4 attacks of wheeze, or ≥1 night per week sleep disturbance from wheeze, or wheeze affecting speech, in the past 12 months; *Shortness of breath*: a composite outcome, positive if children were reported to be breathless during normal daily activities or on minimal exertion; *Any respiratory symptom*: a composite outcome, positive if a participant was reported to have any of the previously described symptom outcomes.

Continuous FEV_1 and FVC values were used in the primary analysis. Standardised z-scores and lower limits of normal for FEV_1, FVC and FEV_1/FVC were derived from the GLI 2012 reference equations for African-Americans, which provide race- and sex-specific reference values, taking into account height and age.[57]

Personal CO exposure monitoring data were not analysed if <24 hours were recorded. To allow comparison of varying lengths of recording, all data were truncated at 24 hours for the final analysis.

Potential effect modifiers included were height (cm), weight (kg), age, and sex.

3.2.6 Study size

We calculated a sample of 600 participants (300 male, 300 female) would estimate the prevalence of non-communicable lung disease (chronic respiratory symptoms) in each sex stratum with a precision (95% CI) of ±3.3 to ±5.0% (assuming a prevalence of 10 to 25%). To allow for unequal sex distributions, refusals and inability to provide spirometry of acceptable quality, we aimed to recruit 1000 children.

3.2.7 Statistical analysis

Descriptive analysis was performed, using Student's t-test and Pearson's chi-square to compare continuous and categorical data. For population proportions, Wald-type standard errors were calculated, assuming a binomial distribution. Bivariate associations between spirometric and clinical outcomes, and variables including CO, COHb, hospital admission for respiratory illness during infancy, and CAPS allocation were explored. Harmonic regression was used to account for any possible effect of seasonality on the outcome measures. This was implemented by including sinusoidal functions (sine and cosine terms) of time with a period of 1 year. Linear multivariable regression was used to estimate the association between exposures and continuous lung function values (FEV_1 and FVC). Multivariable logistic regression models were constructed for dichotomous clinical outcomes. All models included age, sex, height and weight *a priori*, and variables with a p value <0.2 on bivariate analysis. A backward stepwise regression technique was used to develop multivariable models. An analysis was conducted to compare FEV_1, FVC and FEV_1/FVC, symptom prevalence and exposure variables between the intervention and control groups of CAPS. CO was $\log_{10}$ transformed for inclusion in linear models to ensure normality of residuals.

Analyses were conducted using R version 3.4.1 statistical software.[354]

3.2.8 Ethical approval

Ethical approval was given by the College of Medicine Research Ethics Committee in Malawi (reference P.07/16/1994) and Liverpool School of Tropical Medicine Research Ethics Committee in the UK (reference 16-040)

3.3 Results

Between February-December 2017 we approached 886 children of whom 804 were confirmed to be eligible and were recruited (79/82 were outside the eligible age range; 3/82 guardians declined to consent). Questionnaire data were collected for all but one participant who withdrew from the study shortly after giving consent. Anthropometry, spirometry, COHb measurement and personal CO monitoring were done on 99.9% (802/803), 99.9% (802/803), 99.4% (798/803) and 99.3% (797/803) of these participants, respectively. Grade A-C pre-bronchodilator traces were achieved in 65% (522/802) of the children. The duration of CO monitoring was 24 and 48 hours for 91.9% (738/803) and 79.5% (638/803) children, respectively. There were 476 (260 intervention and 216 control) children from households included in CAPS (Figure 3-1).

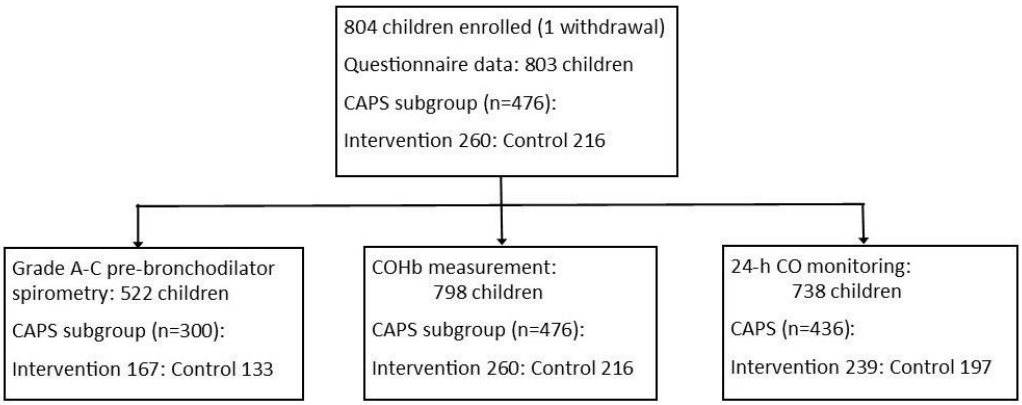

Figure 3-1. CLHS participant recruitment flow diagram

The mean age (SD) of participants was 7.13 (0.77) years and 417 (51.9%) participants were female. Most (700 (87.2%)) were attending primary school. The mean (SD) height-for-age and weight-for-age z-scores were -1.04 (0.90)

and -1.10 (0.89), respectively. Mean (SD) MUAC was 15.98 (1.26) cm (Table 3-2). No children met the criteria for severe or moderate acute malnutrition, but 11/789 (1.4%) children were "at risk for acute malnutrition", with a MUAC of 12.5-13.5cm.

Table 3-2. Demographics and clinical characteristics of CLHS participants (n=803)

	n (%)
Female, n (%)	417 (51.9)
Age, mean (SD) years	7.13 (0.77)
School attendance, n (%)	700 (87.2)
Anthropometry	
Weight-for-age z-score, mean (SD)	-1.10 (0.89)
Height-for-age z-score, mean (SD)	-1.04 (0.90)
MUAC, mean (SD) cm[a]	15.98 (1.26)
Chronic respiratory symptoms	
Wheeze ever	97 (12.1)
Current wheeze (in the past 12 months)	57 (7.1)
Severe asthma (in the past 12 months)	31 (3.9)
Wheeze with exercise	44 (5.5)
Dry cough at night	145 (18.1)
Chronic cough	64 (8.0)
Chronic sputum production	13 (1.6)
Chronic shortness of breath	49 (6.1)
Any chronic respiratory symptom	133 (16.6)

[a] MUAC measurement available for 789 participants

Chronic respiratory symptoms were reported by 133 (16.6% (standard error (SE) 1.3)) children, most commonly cough (8.0% (SE 1.0)), and current wheeze (7.1% (SE 0.9)) (Table 3-2). One-fifth (159/803) of children had been admitted to hospital with respiratory symptoms in the past; on one (9.7%), two (6.1%), and three or more (4.0%) occasions. Admission for a respiratory problem during the first year of life was reported for 70 (8.7%) children. Antibiotic use for a chest problem in the last year was common, reported for 112 (13.9%) children, with 69 (8.6%) receiving these on more than one occasion. Half (54.4%) of children with current wheeze had symptoms of severe asthma, representing 3.9% of children overall. Of these, 22 (71.0%) had a previous hospital admission, and 10 (32.2%) missed school due to breathing problems.

Very few (0.4%) children had previously been treated for tuberculosis, and 2.0% (6/307) of children who had been tested for HIV were HIV-positive.

Children producing grade A-C were older than those with unacceptable traces (mean age 7.23 vs. 6.96 years, p<0.001); otherwise there were no significant differences in growth parameters and respiratory symptoms between the two groups (Table 3-3).

Table 3-3. Comparison of growth measurements and respiratory symptoms for children producing grade A-C and D or F spirometry traces

	A-C n=522	**D, F n=280**	**p value ***
Age, mean (SD) *years*	7.23 (0.78)	6.96 (0.72)	<0.001
Growth parameters			
Weight-for-age z-score, mean (SD)	-1.13 (0.89)	-1.04 (0.87)	0.17
Height-for-age z-score, mean (SD)	-1.04 (0.92)	-1.04 (0.87)	0.93
MUAC, mean (SD) *cm*	15.96 (1.28)	16.02 (1.23)	0.50
Prevalence of chronic respiratory symptoms			
Chronic cough, %	8.6	6.8	0.44
Current wheeze, %	7.3	6.8	0.91
Severe wheeze, %	4.2	3.2	0.61
Chronic SOB, %	6.7	5.0	0.42

*comparison of means using Student's t-test; comparison of proportions using Pearson's chi-squared test

Overall, participants had a mean (SD) FEV_1 z-score -0.48 (0.93) and mean (SD) FVC z-score of -0.30 (0.96). Children from CAPS intervention households had higher FVC z-scores than those from control households (-0.22 vs -0.44, p=0.05). Pre-bronchodilator spirometric abnormalities were found in 68/522 (13.0%) of children; 7.1% with low FVC and 6.3% obstruction (Table 3-4). Post-bronchodilator spirometry was attempted by 706 children, with 72% (505/706) producing grade A-C traces. Both pre- and post-bronchodilator traces were available for 432 children, 26 of whom had a pre-bronchodilator FEV_1/FVC ratio below the LLN which was reversible in 8 (30.7%).

Table 3-4. Pre-bronchodilator lung function parameters for participants with grade A-C spirometry, including the CAPS subgroup.

	Participants with A-C spirometry (n=522)	CAPS intervention (n=167)	CAPS control (n=133)	Intervention vs control *
FEV_1 z-score, mean (SD)	-0.48 (0.93)	-0.41 (0.92)	-0.60 (0.97)	P=0.10
FVC z-score, mean (SD)	-0.30 (0.96)	-0.22 (0.97)	-0.44 (0.98)	P=0.05
FEV_1/FVC z-score, mean (SD)	-0.38 (0.90)	-0.40 (0.91)	-0.34 (0.93)	P=0.57
FVC <LLN, n (%)	37/522 (7.1%)	11/167 (6.6%)	12/133 (9.0%)	P=0.57
Obstructive spirometry FEV_1/FVC <LLN, n (%)	33/522 (6.3%)	11/167 (6.6%)	10/133 (7.5%)	P=0.93
Abnormal spirometry (low FVC, obstruction, mixed), n (%)	68/522[a] (13.0%)	21/167[b] (12.6%)	22/133 (16.5%)	P=0.42

[a] Mixed pattern in 2 participants; [b] Mixed pattern in 1 participant
*comparison of means using Student's t-test; comparison of proportions using Pearson's chi-squared test

Personal CO monitoring showed considerable variation in exposure throughout the monitored period (Figure 3-2).

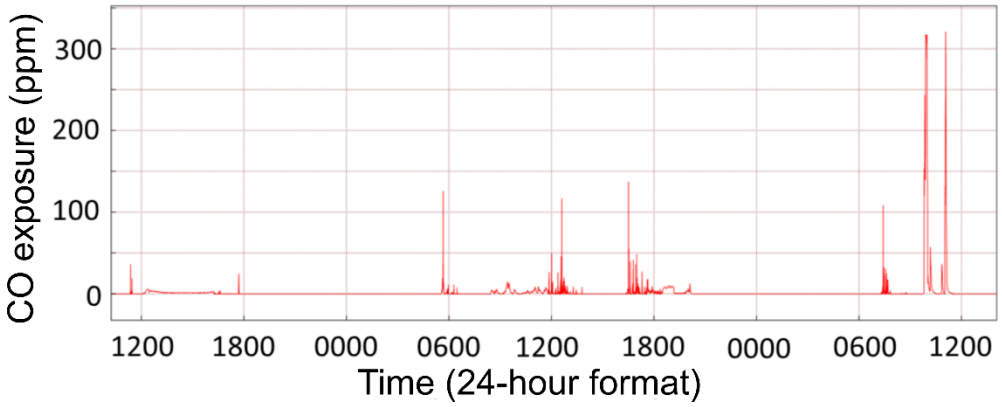

Figure 3-2. Example of a typical 48-hour CO monitoring trace.

Mean exposure levels ranged from 0- 15.1 parts per million (ppm), with a median CO exposure of 0.20 ppm (interquartile range (IQR) 0.07-0.54). Peaks exceeding the 15-minute indoor WHO guideline (81 ppm; 100 mg/m^3) were observed in 370/738 (50.1%) of participants (Figure 3-3).

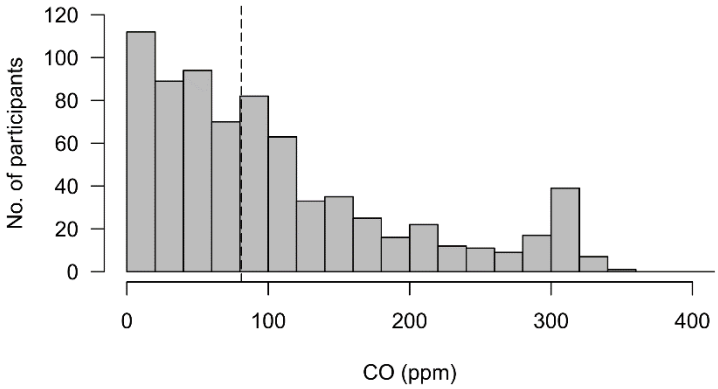

Figure 3-3. Maximum CO levels recorded during monitoring period for 738 participants.

Dashed line represents WHO recommended indoor exposure guideline for a 15-minute time period.[355]

Median %COHb was 4.00 (IQR 1.50-6.50). 68.5% of participants had a level greater than 2%, and 6.0% greater than 10% (Figure 3-4).

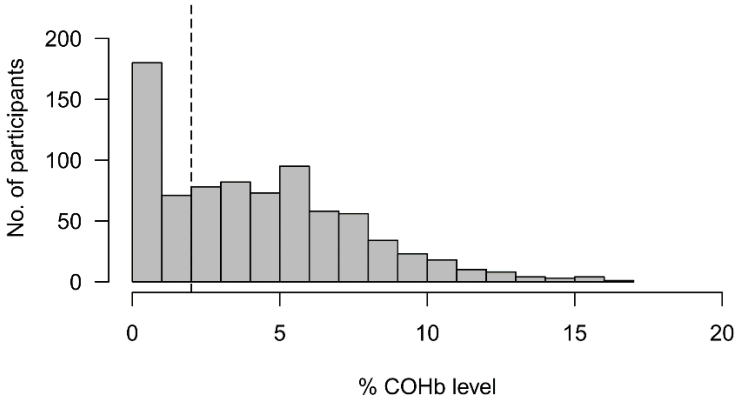

Figure 3-4. %COHb level for 798 participants.

Dashed line represents the WHO COHb guideline.[355]

We found no association between respiratory symptoms or spirometric indices and personal CO and COHb measurements in bivariate analyses and therefore these variables were not carried forward into multivariable analysis. In logistic multivariable analysis, chronic cough (OR 2.63 (95% CI: 1.13, 6.12)), current wheeze (OR 5.48 (95% CI: 2.45, 12.26)) and symptoms of severe asthma (OR 6.36 (95% CI: 2.34, 17.28)) were all associated with hospital admission during infancy (Table 3-5). We found no association between

respiratory symptoms and spirometric indices in bivariate or multivariable analysis (Table 3-5).

Table 3-5. OR (95% CI) for chronic respiratory symptoms estimated by multivariable logistic regression (n=522)

	Cough	Current wheeze	Severe asthma	Shortness of Breath
Age (years)	0.72 (0.48, 1.06)	0.63 (0.40, 0.99)[c]	-	1.43 (0.89, 2.32)
Sex	-	-	-	-
Body Mass Index	-	-	0.65 (0.44, 0.95)[c]	-
Admission during infancy	2.63 (1.13, 6.12)[c]	5.53 (2.49, 12.29)[a]	5.89 (2.20, 15.79)[a]	-
Pre-bronchodilator FEV_1 (l)	-	-	0.16 (0.01-1.90)	0.18 (0.02-1.44)

Significant at; [a] 0.001, [b] 0.01, [c] 0.05 level

In the analysis comparing intervention and control groups, we found statistically significant associations between the intervention arm and both FVC (coefficient estimate 0.04 (95% CI: 0.00, 0.07)), and COHb level (coefficient estimate -0.89 (95% CI: -1.53, -0.26)) (Table 3-6).

We found no significant differences between CAPS arms for growth parameters (Table 3-6) or chronic respiratory symptom rates (Table 3-7).

Table 3-6. CAPS secondary trial analyses: mean or median values, with linear model coefficient estimates (95% CI) for continuous outcomes

	Intervention	Control	Intervention vs control	p-value
FEV_1, mean (SD) *litres*[a]	1.02 (0.18)	0.97 (0.19)	0.02 (-0.01, 0.06)	0.135
FVC, mean (SD) *litres*[a]	1.16 (0.21)	1.09 (0.21)	0.04 (0.00, 0.07)	0.033
FEV_1/FVC, mean (SD) [a]	0.88 (0.06)	0.89 (0.06)	-0.01 (-0.02, 0.01)	0.411
%COHb, median (IQR)[b,e]	3.50 (1.00-6.00)	4.85 (2.00-7.00)	-0.89 (-1.53, -0.26)	0.006
Mean CO *ppm*, median (IQR)[c,e,f,†]	0.18 (0.05-0.55)	0.20 (0.08-0.52)	0.03 (-0.35, 0.42)	0.857
Weight-for-age z-score, mean (SD)[b]	-1.20 (0.89)	-1.06 (0.85)	-0.13 (-0.29, 0.02)	0.096
Height-for-age z-score, mean (SD)[b]	-1.10 (0.84)	-1.06 (0.93)	-0.04 (-0.20, 0.12)	0.624
MUAC, mean (SD) *cm*[d]	15.92 (1.29)	15.94 (1.30)	-0.02 (-0.26, 0.21)	0.846

[a] Spirometry data for 300 participants; 167 intervention, 133 control. FEV_1, FVC and FEV_1/FVC adjusted for age, sex, height and weight in regression model
[b] COHb, height, and weight data for 476 participants; 260 intervention, 216 control
[c] 24-hour CO monitoring for 436 participants; 239 intervention, 197 control
[d] MUAC for 466 participants; 260 intervention, 206 control
[e] Adjusted for seasonality in linear regression model
[f] Log_{10} CO values used in linear regression model
[†] Mean exposure was estimated over the monitoring period per individual, the median of these values (and IQR) is presented for the study population

Table 3-7. CAPS secondary trial analyses: proportions and OR (95% CI) for symptom outcomes (n=476)

	Intervention (n=260)	Control (n=216)	Intervention vs control	p-value
Cough, n (%)	30 (7.7%)	18 (8.3%)	0.92 (0.47-1.78)	0.797
Current wheeze, n (%)	19 (7.3%)	17 (7.9%)	0.92 (0.47, 1.82)	0.817
Severe asthma, n (%)	11 (4.2%)	10 (4.6%)	0.91 (0.38, 2.19)	0.833
Shortness of breath, n (%)	13 (5.0%)	14 (6.5%)	0.75 (0.34, 1.63)	0.471
Any respiratory symptom, n (%)	37 (14.2%)	40 (18.5%)	0.72 (0.44, 1.18)	0.193

3.4 Discussion

This is one of the first studies to report lung function and personal household air pollution exposure, measured concurrently in young children, and it was conducted in the context of the largest trial of a cleaner-burning cookstove intervention to date. Among children living in rural Malawi, we found that; one in six reported chronic respiratory symptoms; over half with current wheeze had severe symptoms; anthropometric and lung function parameters were generally decreased compared to global reference ranges; the majority of children had COHb levels above WHO recommended guidelines; and half of children exceeded WHO guidelines for CO exposure (100mg/m^3), during 24-hour monitoring.[350] Overall, we found no evidence of an association between CO exposure and respiratory symptoms or lung function. However, children from CAPS intervention households had higher FVC z-scores and lower COHb levels than controls.

There are limited data regarding chronic respiratory symptoms in children from Africa, and particularly rural settings. One study from rural Senegal reported similar rates with 9% current wheeze and 5% severe asthma among children aged 5 to 8 years.[72] Studies from urban settings in sub-Saharan Africa, including ISAAC sites, reported rates of current wheeze in 5 to 16% of young children, with symptoms of severe asthma in half of these.[51,69,70,76] Globally 11.5% of children aged 6-7 years have current wheeze, and 4.9% have symptoms of severe asthma; severe symptoms are seen in one third of children with current wheeze in Europe.[51] The high rates of severe symptoms seen in low-income countries are concerning, and likely reflect multiple challenges within healthcare systems, which are better equipped to manage acute episodes relating to infectious diseases, rather than chronic non-communicable conditions. In keeping with this, recent research from Nigeria and South Africa has reported high rates of under-diagnosed and untreated asthma in schoolchildren.[356,357]

We found decreased lung function parameters in this study, comparable to values reported for community controls in a recent study exploring long-term

outcomes after severe acute malnutrition, at the referral hospital in Blantyre, Malawi.[171] Mean (SD) FEV_1 and FVC z-scores were comparable to those of adults from the same community (-0.49 (0.93) and -0.30 (0.96) for children; -0.38 (1.14) and -0.19 (1.09) for adults) adding to evidence that spirometric abnormalities in adults have their origins in early life. These lung function deficits, when compared to international reference ranges, may reflect host and environmental factors such as undernutrition, frequent respiratory infections, low birth weight, exposure to pollutants in utero and early life, which can have adverse effects on lung growth and development.[126,133,134,358,359] No children in this study were acutely malnourished (as defined by MUAC measurement), although other anthropometric parameters (weight- and height-for-age z-scores) were reduced compared to international standards, suggesting a level of chronic undernutrition in this community. There are limited data regarding normal lung function in healthy African paediatric populations, and consequently it is difficult to understand the clinical significance of these apparent spirometric deficits.[173] Further research is needed to describe optimal lung growth in African populations, and determine the morbidity and mortality associated with lung function abnormalities.[66]

Consistent with our previous findings in Chikhwawa, we noted exposure to high peaks of CO, reaching up to three times the WHO guidelines around cooking times, although mean and median levels were low; median CO 1.23 ppm (IQR: 0.79-1.93) in adults and mean CO 1.27 ppm (SD 2.79) in younger children.[23,360] Median CO exposure levels were lower (0.20 ppm (IQR: 0.07-0.54) in our older paediatric population perhaps reflecting long periods of time that children spend away from the home environment during the school day. Cookstove trial analyses exploring adult lung function as a secondary outcome have found no evidence of intervention benefit.[23,233,234] Paediatric lung function outcomes in cookstove trials are inconclusive, but signal a possible beneficial effect of the interventions. Secondary analysis from the RESPIRE trial found decreased lung growth at around 5-years of age

(measured by peak expiratory flow), associated with delayed chimney stove installation, although there was no association between lung function at age 5 and measured personal CO exposure during the first 18 months of life.[361] The GRAPHS birth cohort in rural Ghana recently reported an association between prenatal CO exposure and infant lung function at 30 days of life, with an increased effect of exposure on female infants.[40] Cross-sectional studies from Nigeria have described decreased lung volumes (FEV_1 and FVC) and increased asthma symptoms in children with self-reported exposure to biomass cooking fuels.[357,362]

The association between CAPS intervention group and higher FVC is interesting, given the lack of evidence for an association between lung function and CO exposure or COHb level. This positive finding must be interpreted cautiously as it is the result of exploratory secondary analyses, unadjusted for multiplicity and therefore may be due to chance. However, when taken with the second signal of a potential effect, lower COHb observed in the intervention group, the results may be evidence of a genuine impact. We may have observed a benefit among our participants, who were aged 3-6 years during the CAPS trial period, in contrast to findings from adult populations, because the early childhood years represent a key period for lung development. There is rapid alveolar expansion and resulting lung growth during the first 2 years of life, which stabilises around 8 years of age.[112] Alveolar number is reflected by FVC in childhood and so it is biologically plausible that we might see improved lung function in children from the intervention arm; the apparent difference of 70 ml in mean FVC between CAPS groups represents approximately 6% of a child's lung volume. Furthermore, young children have increased susceptibility to air pollutants, exhibiting increased deposition of particles in the lung, due to physiological and anatomical factors.[195] CO exposure measures do not appear to be associated with lung function or respiratory symptoms – perhaps CO is an inadequate proxy for other pollutants of interest, such as $PM_{2.5}$ and nitrogen dioxide. Our previous air pollution monitoring work in Chikhwawa has

demonstrated that monitored CO exposure correlates weakly with COHb, $PM_{2.5}$ exposure, and measured black carbon in airway cells from induced sputum.[23,360,363]

This study was conducted in the context of the largest cookstove intervention trial to date – a major strength enabling us to assess the effect of a cookstove intervention on childhood spirometry and air pollution exposure outcomes. Cookstove use declined during the CAPS follow-up period, with one-quarter of households using the cookstoves for two or more meals per day after 24-months. Cookstove and solar panel malfunctions were common, with four repairs/replacements per intervention household during the 2-year trial period.[26] It seems unlikely that many households would continue to use the cookstoves in 2017, without the maintenance support provided by the trial: from anecdotal reports however, we believe that increased awareness of the adverse effects of smoke led to altered cooking behaviours among study staff and participants. These altered behaviours, such as cooking away from the house and in better ventilated areas may have been responsible for the lower COHb observed in our "intervention" participants.

Other strengths of this study include high participation rates for spirometry and CO exposure monitoring, and good quality spirometry in a representative sample of children, despite the highly challenging research environment of a rural area in a low-income country. We achieved our sample size, even though field work was disrupted by vampirism hysteria in the community; periodically there are reports of "blood-suckers" in Malawi – people are fearful of strangers during these times and research activities were suspended to avoid fuelling the mass hysteria, particularly those studies collecting samples or using unfamiliar equipment We acknowledge limitations to our study including that personal monitoring of CO for 48 hours provides only a snapshot of exposure to a single pollutant. There are substantial limitations to the methods currently available for monitoring personal exposure to other pollutants in this young age group; the Lascar CO-monitoring device represents one of the best options available, at present. Monitoring during a

48-hour exposure period may not describe individual variation in daily and seasonal routines but reflected a compromise in terms of feasibility and acceptability in this large study population. Questionnaire data may have been subject to recall bias, with limited information on contributing factors such as birthweight, gestation at birth, HIV-status, and exposure to passive smoking.

In conclusion, the substantial burden of chronic respiratory symptoms, abnormal spirometry and air pollution exposures in children in rural Malawi is concerning and calls for strategies to maximise healthy lung development and to effectively manage chronic respiratory conditions. To achieve this, research will be needed to develop ways to increase awareness of non-communicable lung diseases, such as asthma, at a community level to inform health care seeking behaviours and ensure access to appropriately trained health care providers and effective long-term treatment such as inhaled medication. Our finding of a potential beneficial effect of a cleaner burning biomass-fuelled cookstove on lung function (FVC) calls for further research into clean-air initiatives, tackling multiple sources of air pollution in a community-wide approach to promote lung health in children.

3.5 List of appendices for chapter 3

- Ethical approval from College of Medicine Research Ethics Committee (Malawi)
- Ethical approval from Liverpool School of Tropical Medicine (UK)
- Participant information sheet – English
- Consent form – English
- Questionnaire – English
- Chichewa versions of study documents and SOPs available on request;
    - SOP – data collection
    - SOP – COHb measurement with Rad57
    - SOP – Spirometry
    - SOP – CO measurement with EasyLog

4 Non-communicable respiratory disease and air pollution exposure in Malawi: a prospective cohort study

4.1 Introduction

Non-communicable respiratory diseases including chronic obstructive pulmonary disease (COPD) and asthma are a growing global concern, particularly in low- and middle-income countries (LMIC).[53,43,87] Air pollution, including exposure to tobacco smoke, outdoor and household air pollutants, and occupational exposure to dust and fumes, is considered a major risk factor for non-communicable respiratory disease development and exacerbations.[53,190] However, conflicting findings from recent studies have cast uncertainty over the specific role of household air pollution in COPD development.[96,231] Approximately 3 billion people worldwide rely on highly polluting biomass fuels for cooking, heating and lighting.[350] It is therefore a global public health priority to better understand the impact of household air pollution on non-communicable respiratory disease morbidity and mortality.

The lung function trajectories of adults from sub-Saharan Africa (sSA) are largely undescribed; limited published data relate to cohorts from South Africa with HIV-infection and occupational silica dust exposure.[239,364] There are no data from population-representative cohorts in sSA; it is not known whether adults exposed to biomass-related air pollution would experience accelerated age-related decline in lung function and therefore an increased risk of developing obstructive airways diseases as occurs in those exposed to tobacco smoke.[220,222]

The cross-sectional BOLD (Burden of Obstructive Lung Disease) study, conducted in urban Blantyre, Malawi found unexpectedly high rates of decreased FVC and high levels of self-reported exposure to biomass smoke.[22] The finding of a high burden of low FVC was concerning given the association between this and increased mortality.[24] To further explore this phenomenon, we did a second study in rural Chikhwawa, Malawi (entitled BOLD-

Chikhwawa) with the same protocol as the Blantyre BOLD study, but with the addition of measurement of personal exposure to air pollutants: carbon monoxide (CO) and fine particulate matter ≤2.5µm ($PM_{2.5}$).[23] We found comparably high rates of spirometric abnormalities, with decreased FVC seen in 35% of participants, but no association between spirometric outcomes and exposure to CO or $PM_{2.5}$ despite high levels of air pollution. Participants were from village communities which also participated in the Cooking and Pneumonia Study (CAPS), a cluster randomised trial of a cleaner-burning biomass-fuelled cookstove.[26] Secondary analysis of adults from a sub-set of CAPS households found no difference in respiratory symptoms, lung function or personal air pollution exposures between intervention and control groups, but these analyses were done using cross-sectional data that were collected only a short time after introduction of the intervention – it is not known whether the rate of decline in lung function over time would be different between the trial arms.[23]

This longitudinal study, the Adult Lung Health Study (ALHS) reports lung function and personal air pollutant exposure measurements from 3-years of follow-up for the BOLD-Chikhwawa cohort, to explore the determinants of lung function trajectories, including the effect of the CAPS cookstove intervention, in adults living in rural Malawi.

4.2 Methods

4.2.1 Setting

Chikhwawa is a rural district, approximately 50km south of Blantyre, on the Shire river valley. During the study period, this district experienced severe flooding and crop failures. CAPS recruited children aged <4.5 years in Chikhwawa between December 2013 and August 2015; intervention households received two cleaner-burning biomass-fuelled cookstoves, a solar panel to charge the stove-fan battery and user training at the time of randomisation. Those in the control arm continued using traditional cooking methods, mostly open fires, but received cookstoves at the end of the CAPS follow-up in May 2016.

BOLD-Chikhwawa was a separate study, recruiting adults from the same village communities as CAPS: not all BOLD-Chikhwawa participants were enrolled in CAPS. Figure 4-1 shows the timeline of CAPS and BOLD-Chikhwawa activities.

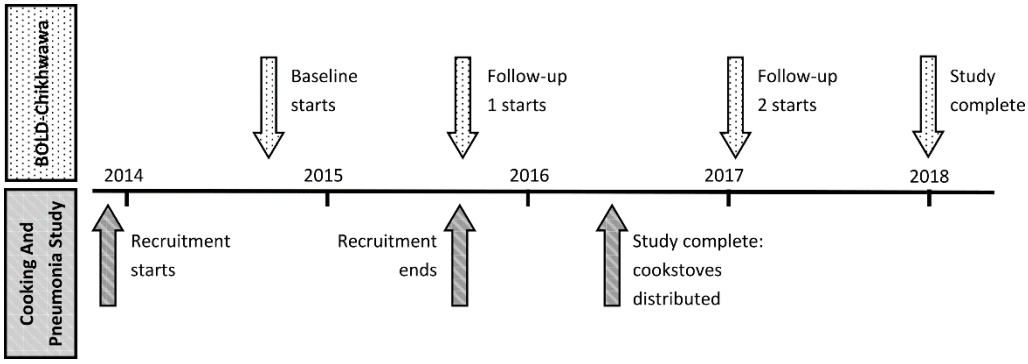

Figure 4-1. Timeline showing CAPS and BOLD-Chikhwawa activities

4.2.2 Participants

Following community engagement events, a list of all adults living in each of the 50 villages participating in CAPS in Chikhwawa was obtained from local community health workers. An independent statistician at the BOLD-centre in London used these collated lists to obtain a population-representative sample of adults aged >18 years, stratified by age and sex. All potential participants were invited to participate, with information provided in the local language, Chichewa, and written informed consent (or witnessed thumbprint) obtained from those who agreed.[23]

4.2.3 Procedures

Fieldworkers conducted follow-up visits in the community, approximately one and two years after enrolment, according to BOLD study standardised operating procedures, to collect questionnaire, spirometry and personal air pollution exposure data.[21] Fieldworkers administered an abbreviated version of the BOLD study questionnaire in Chichewa, and measured height and weight.

BOLD-centre certified fieldworkers conducted spirometry according to European Respiratory Society /American Thoracic Society (ERS/ATS) standards

using an EasyOne Spirometer (ndd Medical Technologies; Zurich, Switzerland), before and after administration of 200 micrograms of Salbutamol via Volumatic spacer.[58] Spirometry overreading was performed by an independent technician, according to the BOLD criteria for acceptability and repeatability.

After completing the questionnaire and spirometry assessment, participants were given an Indoor Air Pollution (IAP) 5000 Series Monitor (Aprovecho Research Centre, Oregon, USA) which they were instructed to wear in a small backpack during the day and to keep beside their sleeping mat at night, to estimate personal exposure to $PM_{2.5}$ and CO over a 48 hour period. These monitors continuously sample air from the breathing zone, and $PM_{2.5}$ and CO are measured using a light-scattering photometer and electrochemical cell CO sensor, respectively. Fieldworkers encouraged compliance with personal exposure monitoring during frequent community visits. IAP traces with outlying $PM_{2.5}$ or CO values (extremely high or low) were visually inspected for expected daily variation in exposure: traces without variability, suggesting that backpacks had not been worn, were excluded from the analysis.

4.2.4 Variables

Clinical outcomes were assessed by the questions detailed in Table 4-2. Raw FEV_1 and FVC values were used as continuous variables in the longitudinal analysis. Lung function parameters were compared with age, sex and height-standardised Global Lung Initiative (GLI) reference ranges for African-Americans and NHANES III reference ranges for Caucasians and African-Americans.[57,61] Restriction was defined as FVC below the lower limit of normal (LLN), and obstruction as FEV_1/FVC ratio below the LLN; values below the 5^{th} centile in a healthy, non-smoking reference population.

Exposures included estimated personal exposure to $PM_{2.5}$ and CO, and questionnaire assessment of smoking status and previous tuberculosis. At baseline, first and second follow-up, participants were classed as having access to a cookstove if their household had been given a cleaner-burning biomass-fuelled cookstove by the CAPS study team prior to data collection.

Baseline $PM_{2.5}$ and CO levels were zeroed at the 0.1th percentile of values obtained during each monitoring period. Observations were included if >24-hours were recorded, with recording truncated into 24-hour periods to reflect daily variation in personal exposure patterns, and only full 24-hour periods analysed. Log mean 24-hour $PM_{2.5}$ and CO estimates were used for mixed-effects modelling.

Potential effect modifiers: Body Mass Index (BMI) and/or height and weight, age, years of education and sex, were evaluated as fixed covariates in the FEV_1 and FVC linear mixed-effects models.

4.2.5 Study size

3000 adults were initially invited to enrol in the baseline BOLD-Chikhwawa cohort. Participants were followed up if they had completed a baseline questionnaire (1481 participants) and were included in the longitudinal lung function analysis if they had at least two valid spirometry assessments during the study period.

4.2.6 Statistical methods

Descriptive analysis was performed, with Student's t-test and Pearson's chi-square to compare continuous and categorical data.

Participants with incomplete data (lost-to-follow-up or failing to complete spirometry) were compared to those with complete data using chi-square and Student's t-test. Positive associations ($p<0.2$) on bivariate analysis were explored in multivariable logistic regression.

Two separate mixed-effects models were developed for analysis of repeated exposure and lung function outcomes. In the log-linear exposure models, repeated estimates (mean 24-hour CO and $PM_{2.5}$) from individuals were accounted for using an individual level random effect, with an additional random-effect accounting for clustering of 24-hour measurements within 48-hour monitoring periods. Fixed effect covariates were selected sequentially to determine the optimum model fit by likelihood ratio testing under maximum likelihood estimation (MLE), with calculation of parameter estimates,

standard errors and p-values. Harmonic terms were included in the exposure models to account for any possible effect of seasonality on the outcome measures. This was implemented by including sinusoidal functions (sine and cosine terms) of time with a period of 1 year.

Longitudinal lung function (FEV_1 and FVC) linear models included the fitted CO and $PM_{2.5}$ values from the exposure model as fixed covariates; an average value was calculated where participants had multiple periods of exposure monitoring. Fixed effect covariates were sequentially assessed by likelihood ratio testing under MLE, with interaction terms to explore the change in lung function over time. The final regression equations used in the exposure and lung function analysis are included in section 4.2.7. Analyses were conducted using R version 3.4.1 statistical software.

4.2.7 Regression equations for mixed-effects exposure models

4.2.7.1 *CO model*

$$logY_{ijt} = \alpha + b_{ijt}\beta_1 + c_{ijt}\beta_2 + d_{ijt}\beta_3 + e_{ijt}\beta_4 + U_i + V_{ij} + Z_{ijt}$$

where:

Y_{ijt} = exposure measurement for participant *i*, during 48-hr monitoring period *j*, on day *t*

$\beta_1, \beta_2, \beta_3, \beta_4$ = fixed effects parameter estimates

b = sex (female=1, male=0)

c = current smoker (yes=1, no=0)

$d = \cos\left(\frac{2\pi}{365} * \text{day of year}\right)$

$e = \sin\left(\frac{2\pi}{365} * \text{day of year}\right)$

$U_i \sim N(0, \sigma_u^2)$, random effect for the *i*th participant

$V_{ij} \sim N(0, \sigma_v^2)$, random effect for *j*th 48-hour monitoring period in the *i*th participant

$Z_{ijt} \sim N(0, {\sigma_x}^2)$, error term associated with the *t*th measurement in the *j*th 48-monitoring period for the *i*th participant.

4.2.7.2 $PM_{2.5}$ model

$$logY_{ijt} = \alpha + b_{ijt}\beta_1 + c_{ijt}\beta_2 + U_i + V_{ij} + Z_{ijt}$$

where:

Y_{ijt} = exposure measurement for participant *i*, during 48-hr monitoring period *j*, on day *t*

β_1, β_2 = fixed effects parameter estimates

b = sex (female=1, male=0)

c = access to cookstove (yes=1, no=0)

$U_i \sim N(0, \sigma_u^2)$, random effect for the *i*th participant

$V_{ij} \sim N(0, \sigma_v^2)$, random effect for the *j*th 48-hour monitoring period in the *i*th participant

$Z_{ijt} \sim N(0, {\sigma_x}^2)$, error term associated with the *t*th measurement in the *j*th 48-monitoring period for the *i*th participant.

4.2.7.3 FEV_1 and FVC models

$$Y_{it} = \alpha + b_{it}\beta_1 + c_{it}\beta_2 + d_{it}\beta_3 + e_{it}\beta_4 + f_{it}\beta_5 + g_{it}\beta_6 + U_i + Z_{it}$$

where:

Y_{ijt} = lung function measurement for participant *i*, on day *t*

$\beta_1, \beta_2, \beta_3, \beta_4, \beta_5, \beta_6$ = fixed effects parameter estimates

b = time in years

c = age in years

d = sex (female=1, male=0)

e = height in cm

f = previous tuberculosis (yes=1, no=0)

g = Body Mass Index in kg/m^2

$U_i \sim N(0, \sigma_u^2)$, random effect for the *i*th participant

$Z_{it} \sim N(0, {\sigma_x}^2)$, error term associated with the *t*th measurement for the *i*th participant.

4.2.8 Ethical approval

The study was approved by Malawi College of Medicine Research Ethics Committee (reference P.11/12/1308) and the Liverpool School of Tropical Medicine Research Ethics Committee (reference 12.40).

4.3 Results

Between August 2014 and July 2015, 1481 adults were enrolled in the study at baseline and followed up on two subsequent occasions.[23] Three-quarters (75%, n=1090) were re-assessed during the first follow-up period (August 2015–November 2016) and two-thirds (67%, n=989) during the second follow up period (January 2017-November 2017) with data collected as shown in Figure 4-2.

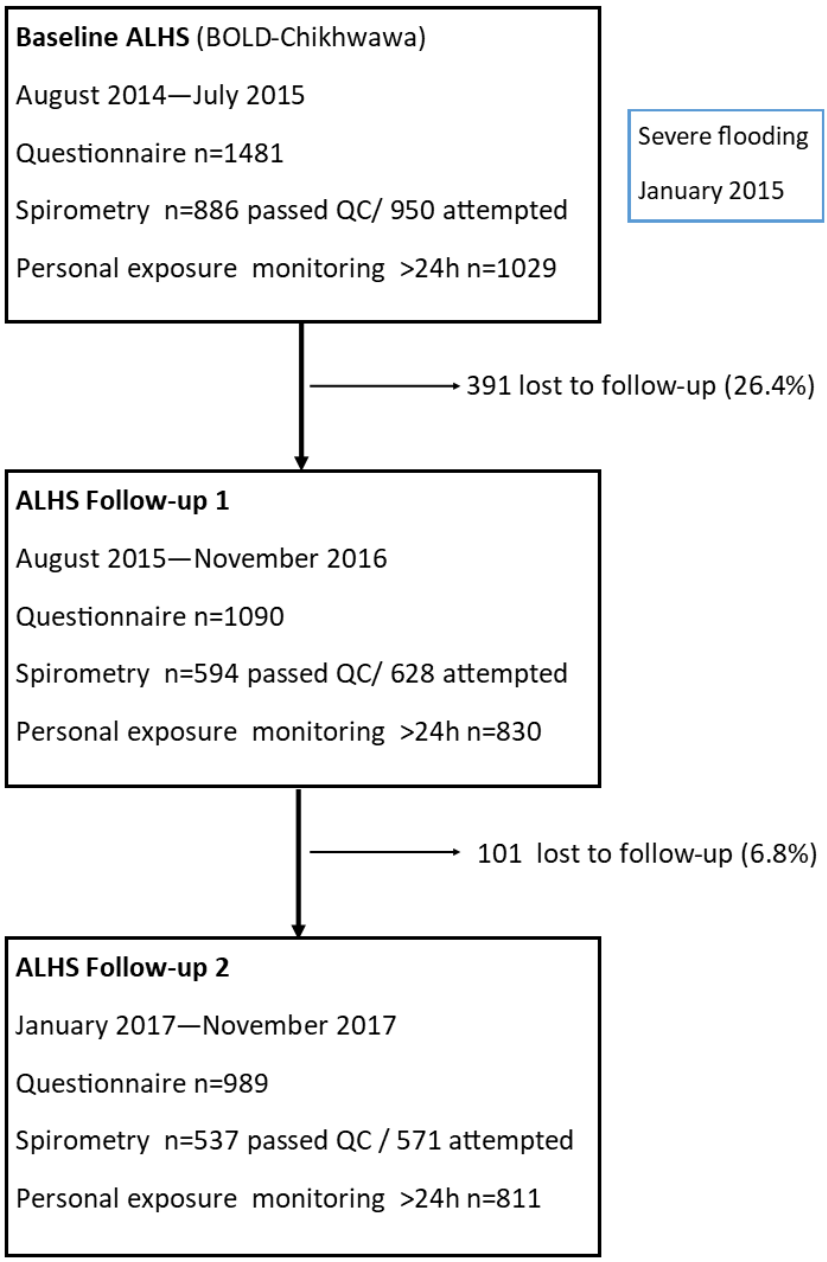

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Figure 4-2. Participant flow diagram.

Demographic data for participants with or without questionnaire, spirometry or exposure monitoring are shown in Table 4-1. Participants completing the second follow-up visit were more likely to be female (odds ratio (OR) (95% CI), 1.88 (1.50-2.37), and to have spent fewer years in education (OR (95% CI), 0.96 (0.93-0.99)).

Table 4-1. Availability of data (questionnaire, exposure monitoring and spirometry) for 1481 participants at baseline, first and second follow-up.

	Data available				**Data not available**		
	n	Mean age (SD)	Sex (% female)	Percent missing from baseline	n	Mean age (SD)	Sex (% female)
Questionnaire							
Baseline	1481	43.8 (17.8)	57.0	-	-	-	-
Follow-up 1	1090	43.6 (17.5)	60.6	26.4	391	44.5 (18.5)	46.8
Follow-up 2	989	44.0 (17.6)	62.9	33.2	492	43.5 (18.2)	45.1
Exposure monitoring							
Baseline	1029	44.0 (17.9)	57.1	30.5	452	43.4 (17.4)	56.6
Follow-up 1	830	44.0 (17.4)	61.8	44.0	651	43.7 (18.3)	50.8
Follow-up 2	811	44.4 (17.2)	62.3	45.2	670	43.2 (18.4)	50.6
Any measurement	1330	44.0 (17.7)	58.6	10.2	151	42.5 (18.1)	42.4
Multiple measurements	929	44.2 (17.5)	61.0	37.3	552	43.3 (18.1)	50.2
Spirometry							
Baseline	886	40.9 (15.3)	51.1	40.2	595	48.2 (20.2)	65.7
Follow-up 1	594	39.0 (14.1)	51.5	59.9	887	47.1 (19.2)	60.7
Follow-up 2	537	37.1 (13.8)	55.5	63.7	944	47.7 (18.6)	57.8
Any measurement	1086	40.2 (15.3)	53.3	26.7	413	53.2 (20.1)	66.6
Multiple measurements	654	38.4 (14.0)	52.0	55.8	827	48.1 (19.2)	60.9

Spirometry was attempted by 950/1481 (64%), 628/1090 (58%) and 571/989 (58%), and personal air pollution exposure monitoring completed for 1029/1481 (69%), 830/1090 (76%) and 811/989 (82%) at baseline, first and second follow-up, respectively (Figure 4-2). Multiple spirometry measurements were available for 654/1481 (44%) of participants whilst 413

(28%) had only one spirometry measurement and 413 (28%) had none. Personal air pollution exposure was estimated on more than one occasion for 929/1481 (63%) of participants whilst 401 (27%) had only one episode of monitoring and 151 (10%) had none.

At baseline, the cohort included 424 participants from CAPS households: this rose to 523 participants (271 from intervention and 252 from control households) as CAPS continued to recruit until August 2015.

The baseline demographics of the cohort have been previously reported.[23] In brief, at baseline the mean (SD) age of participants was 43.8 (17.8) years, 57% were female and all households (99.8%) used biomass fuels for cooking. One third had never attended school and half had not been educated beyond primary school level.

The frequency of reported respiratory symptoms increased greatly over the course of the study (Table 4-2): overall 13.6% (95% CI, 11.9-15.4) of participants reported respiratory symptoms at baseline compared to 36.2% (95% CI, 33.3-39.4) at final follow-up. Self-reported rates of smoking and TB did not change over time; current smoking was reported by 13.9% and 12.9%, and previous TB infection reported by 3.2% and 2.6%, at baseline and final follow-up, respectively.

Table 4-2. Respiratory symptoms and exposures reported by participants at baseline, first and second follow-up.

	% (95% CI)		
	Baseline (n=1481)	**Follow-up 1 (n=1090)**	**Follow-up 2 (n=989)**
Respiratory symptoms			
Cough: Do you usually cough when you don't have a cold?	11.1 (9.6-12.9)	10.1 (8.4-12.0)	25.3 (22.6-28.1)
Sputum: Do you usually bring up phlegm from your chest when you don't have a cold?	2.6 (1.8-3.5)	4.9 (3.7-6.3)	11.1 (9.2-13.2)
Wheeze: Have you had wheezing/whistling in your chest in the last 12-months, in the absence of a cold?	1.6 (1.0-2.3)	1.7 (1.0-2.6)	3.0 (2.1-4.3)
MRC dyspnoea II: Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill?	1.6 (1.0-2.3)	6.6 (5.2-8.2)	11.8 (9.9-14.0)
Functional limitation: Have breathing problems interfered with your usual daily activities?	2.9 (2.1-3.9)	5.7 (4.4-7.2)	7.1 (5.6-8.9)
Any respiratory symptom (any of the above 5 symptoms)	13.6 (11.9-15.4)	19.6 (17.3-22.1)	36.2 (33.3-39.4)
Self-reported exposures			
Current smoker	13.9 (12.2-15.8)	11.6 (9.7-13.6)	12.9 (10.9-15.2)
Previous TB	3.2 (2.3-4.2)	3.0 (2.1-4.2)	2.6 (1.7-3.8)

4.3.1 Personal exposure monitoring

A total of 1768 personal exposure monitoring episodes lasted >48 hours, and a further 902 lasted between 24 and 48 hours. Within episodes of >48 hours, there was fair correlation between the first and second 24-hour periods, for both $PM_{2.5}$ (adjusted R^2=0.68) and CO (adjusted R^2=0.59). Correlation between exposures to the two air pollutant measures (mean $PM_{2.5}$ and CO), analysed for a total of 4438 24-hour monitoring periods was poor (adjusted R^2=0.027).

Overall, the 24-hour median personal $PM_{2.5}$ and CO exposures were 77.0 $\mu g/m^3$ (interquartile range [IQR], 42.8-153.1) and 1.27 ppm (IQR, 0.79-2.05),

respectively. Personal $PM_{2.5}$ (median (IQR)) was 71.7 µg/m^3 (42.8-128.0), 84.6 µg/m^3 (45.9-175.7) and 75.9 µg/m^3 (40.1–176.4) at baseline, first and second follow-up, respectively. Personal CO exposure (median (IQR)) was 1.26 (0.79-2.07) ppm, 1.33 (0.81-2.22) ppm and 1.22 (0.75-1.90) ppm, at baseline, first and second follow-up, respectively.

In total, 4377 24-hour monitoring periods with complete covariate data from 1304 individuals were included in mixed effects exposure models, with CO and $PM_{2.5}$ as the response variables. In the final CO model, we found strong evidence that female sex, current smoking status and seasonality were associated with CO level (Tables 4-3 and 4-4). In the final $PM_{2.5}$ model, female sex was associated with increased $PM_{2.5}$ and access to a cookstove with decreased $PM_{2.5}$ (risk ratio 0.85 (95% CI, 0.75-0.97) (Tables 4-3 and 4-5).

Table 4-3. Estimated risk ratios and 95% confidence intervals for fixed effects covariates included in final air pollutant exposure log linear mixed-effect models

	$PM_{2.5}$ (µg/m^3)	**CO (ppm)**
Sex	1.27 (1.13, 1.42)	1.60 (1.51,1.72)
Current smoking	-	1.22 (1.12, 1.34)
Seasonality: cosine function	-	0.85 (0.81, 0.89)
Seasonality: sine function	-	0.99 (0.96, 1.03)
Access to cookstove	0.85 (0.75, 0.97)	-

Table 4-4. Likelihood ratio comparison of increasingly complex mixed-effects logCO response models

	Fixed effects parameters	*Comparison*	*LogLikelihood*	*Likelihood ratio test*	*df*	*p-value*
1	None	-	-4371.4			
2	Seasonality	1,2	-4344.8	53.2	2	<0.001†
3	Seasonality, sex	2,3	-4256.2	177.2	1	<0.001†
4	Seasonality, sex, age	3,4	-4256.1	0.1	1	0.768
5	Seasonality, sex, smoker	4,5	-4246.6	19.1	1	<0.001†
6	Seasonality, sex, smoker, cookstove	5,6	-4246.5	0.2	1	0.698

†Significant at 0.05 level and included in final model. Final fixed effects covariates highlighted in grey.

Table 4-5. Likelihood ratio comparison of increasingly complex mixed-effects log$PM_{2.5}$ response models

	Fixed effects parameters	*Comparison*	*LogLikelihood*	*Likelihood ratio test*	*df*	*p-value*
1	None	-	-6923.7			
2	Seasonality	1,2	-6923.2	1.1	2	0.574
3	Sex	1,3	-6915.4	16.7	1	<0.001†
4	Sex, age	3,4	-6914.7	1.3	1	0.256
5	Sex, smoker	3,5	-6913.6	3.4	1	0.064
6	Sex, cookstove	3,6	-6912.2	6.2	1	0.013†

†Significant at 0.05 level and included in final model. Final fixed effects covariates highlighted in grey.

4.3.2 Spirometry

Of those attempting spirometry, ERS/ATS standards were achieved by 886/950 (93.3%), 594/628 (94.6%) and 537/571 (94.0%) at baseline, first and second follow-up visits, respectively (Figure 4-2). On bivariate analysis, factors associated with failing to complete spirometry were: older age, lower BMI, female sex, current smoking, cough or any respiratory symptoms. In logistic multivariable analysis, participants who were female (OR (95% CI), 0.52 (0.39-0.71)), older (OR (95% CI), 0.97 (0.96-0.98)) or with a lower BMI (OR (95% CI), 1.09 (1.04-1.14)) were significantly less likely to complete spirometry. Participants with longitudinal spirometry data had reduced lung function at baseline, compared to those who performed spirometry on only one occasion: mean (SD) FEV z-score -0.48 (1.03) vs -0.22 (1.28), mean (SD) FVC z-score -0.33 (1.01) vs 0.03 (1.19), respectively.

Best post-bronchodilator traces were analysed for 1068 participants who completed at least one spirometry session to ERS/ATS standards. Overall, mean (SD) FEV_1 and FVC were 2.55 (0.64) litres and 3.16 (0.73) litres, respectively, with a mean (SD) FEV_1/FVC ratio of 0.80 (0.09) (Table 4-6). When compared to GLI African-American reference ranges, mean (SD) FEV_1, FVC and FEV_1/FVC ratio z-scores were -0.38 (1.14), -0.19 (1.09) and -0.37 (1.04), respectively, with spirometric obstruction seen in 11.2% (95% CI, 9.4-13.2%) and low FVC in 8.1% (95% CI, 6.5-9.9%). Rates of obstruction were similar

when NHANES Caucasian reference ranges were used (11.5% (95% CI, 9.6-13.5%)), but considerably more - approximately 50% - of participants were classified as having a low FVC (49.7% (95% CI, 46.7-52.8%).

Table 4-6. Best post-bronchodilator spirometry values* and classification by GLI and NHANES reference ranges for 1068 participants.

Spirometry value		
Raw	Mean (SD) FEV_1, litres	2.55 (0.64)
	Mean (SD) FVC, litres	3.16 (0.73)
	Mean (SD) FEV_1/FVC ratio	0.80 (0.09)
Z-scores†	Mean (SD) FEV_1 z-score	-0.38 (1.14)
	Mean (SD) FVC z-score	-0.19 (1.09)
	Mean (SD) FEV_1/FVC ratio z-score	-0.37 (1.04)
Classification		% of population (95% CI)
Obstruction	FEV_1/FVC <LLN GLI African American	11.2 (9.4-13.2)
	FEV_1/FVC <LLN NHANES African American	11.5 (9.6-13.5)
	FEV_1/FVC <LLN NHANES Caucasian	9.8 (8.1-11.7)
Restriction	FVC <LLN GLI African American	8.1 (6.5-9.9)
	FVC <LLN NHANES African American	7.7 (6.2-9.5)
	FVC <LLN NHANES Caucasian	49.7 (46.7-52.8)

*For participants with spirometry measured at more than one timepoint, the best FEV_1 and FVC values were analysed
† z-scores calculated using GLI African-American reference ranges

Overall, the annual rate of lung function decline was 30.9ml (95% CI, 21.6-40.1) for FEV_1 and 38.3ml (95% CI, 28.5-48.1) for FVC (Table 4-7). Age, sex, height, previous TB infection, and BMI were included in the final mixed-effects models as significant fixed effect covariates for FEV_1 and FVC (all $p<0.001$, Tables 4-8 and 4-9), although they did not affect rate of lung function decline. Current smoking, access to a cookstove, $PM_{2.5}$ and CO exposure levels did not significantly improve either model. Decreased FEV_1 and FVC were associated with increasing age, female sex, previous TB infection and decreased height and BMI (Table 4-7).

Table 4-7. Parameter estimates for multiple fixed-effects covariates included in final FEV_1 and FVC linear mixed-effect models*.

	FEV_1 ml		**FVC ml**	
	Estimate	**95% CI**	**Estimate**	**95% CI**
Time (years)	-30.9	-40.1, -21.6	-38.3	-48.1, -28.5
Age (years)	-18.7	-20.4, -16.9	-11.0	-13.0, -9.1
Sex (female)	-500.1	-566.6, -433.6	-678.0	-751.4, -604.7
Height (cm)	23.6	19.9, 27.3	32.8	28.7, 36.9
Previous TB (yes)	-404.9	-539.7, -230.2	-334.2	-526.6, -141.8
BMI	21.9	13.8, 30.0	21.3	12.4, 30.2

*Models include post-bronchodilator FEV_1 and FVC data from 950 individuals, including 654 with two or more lung function measurements

Table 4-8. Comparison of increasingly complex mixed-effects FEV_1 response models

	Fixed effects parameters	*Comparison*	*Log Likelihood*	*Likelihood ratio test*	*df*	*p-value*
0	None	-	-13723	-	-	-
1	Time	0,1	-13704	38.7	1	<0.001†
2	Time, age	1,2	-13602	203.0	1	<0.001†
3	Time, age, sex	2,3	-13379	446.0	1	<0.001†
4	Time, age, sex, height	3,4	-13312	134.7	1	<0.001†
5	Time, age, sex, height, smoker	4,5	-13310	3.2	1	0.072
6	Time, age, sex, height, TB	4,6	-13299	25.5	1	<0.001†
7	Time, age, sex, height, TB, BMI	6,7	-13285	28.9	1	<0.001†
8	Time, age, sex, height, TB, BMI, years at school	7,8	-13284	1.3	1	0.248
9	Time, age, sex, height, TB, BMI, cookstove	7,9	-13285	0.14	1	0.706
10	Time, age, sex, height, TB, BMI, CO	7,10	-13285	0.08	1	0.777
11	Time, age, sex, height, TB, BMI, PM	7,11	-13284	2.1	1	0.146
12	Time, age, sex, height, TB, BMI, time*age	7,12	-13284	0.87	1	0.352
13	Time, age, sex, height, TB, BMI, time*sex	7,13	-13285	0.12	1	0.726
14	Time, age, sex, height, TB, BMI, time*TB	7,14	-13285	0	1	0.998
15	Time, age, sex, height, TB, BMI, time*PM	7,15	-13283	2.94	2	0.230
16	Time, age, sex, height, TB, BMI, time*CO	7,16	-13284	0.34	2	0.842

†Significant at 0.05 level and included in final model.

Final fixed effects covariates highlighted in grey.

BMI, body mass index; CO, carbon monoxide; PM, particulate matter; TB, tuberculosis

Table 4-9. Comparison of increasingly complex mixed-effects FVC response models

	Fixed effects parameters	*Comparison*	*Log Likelihood*	*Likelihood ratio test*	*df*	*p-value*
0	None	-	-13912	-	-	-
1	Time	0,1	-13885	54.08	1	<0.001†
2	Time, age	1,2	-13862	45.96	1	<0.001†
3	Time, age, sex	2,3	-13560	604.00	1	<0.001†
4	Time, age, sex, height	3,4	-13454	212.11	1	<0.001†
5	Time, age, sex, height, smoker	4,5	-13454	0.08	1	0.775
6	Time, age, sex, height, TB	4,6	-13446	15.04	1	<0.001†
7	Time, age, sex, height, TB, BMI	6,7	-13435	22.69	1	<0.001†
8	Time, age, sex, height, TB, BMI, years at school	7,8	-13435	0.001	1	0.973
9	Time, age, sex, height, TB, BMI, cookstove	7,9	-13435	0.12	1	0.732
10	Time, age, sex, height, TB, BMI, CO	7,10	-13434	1.89	1	0.170
11	Time, age, sex, height, TB, BMI, PM	7,11	-13434	1.33	1	0.249
12	Time, age, sex, height, TB, BMI, time*age	7,12	-13433	3.34	1	0.068
13	Time, age, sex, height, TB, BMI, time*sex	7,13	-13435	0.08	1	0.78
14	Time, age, sex, height, TB, BMI, time*TB	7,14	-13434	0.79	1	0.37
15	Time, age, sex, height, TB, BMI, time*PM	7,15	-13434	2.70	2	0.259
16	Time, age, sex, height, TB, BMI, time*CO	7,16	-13434	1.96	2	0.376

†Significant at 0.05 level and included in final model.

Final fixed effects covariates highlighted in grey.

BMI, body mass index; CO, carbon monoxide; PM, particulate matter; TB, tuberculosis

4.4 Discussion

This is the first prospective cohort study to report longitudinal lung function and personal exposure to air pollution in a sub-Saharan African population. The main findings were that: FEV_1 and FVC were determined by age, sex, height, previous TB and BMI, whilst there was no evidence of accelerated lung function decline (30.9ml FEV_1 and 38.3ml FVC annual decrease) as might have been expected in this population compared to the natural age-related decline reported in populations from Europe and the USA.[222] Mean (SD) FEV_1 and FVC z-scores (-0.38 (1.14) and -0.19 (1.09)) were comparable to those previously reported for children from this community adding to evidence that spirometric abnormalities in adults have their origins in early life.[365] Lung function was not associated with exposure to CO, $PM_{2.5}$ or access to a cookstove. Estimated CO and $PM_{2.5}$ correlated poorly and were associated with different covariates. Exposure to $PM_{2.5}$ was increased in females and decreased by a factor of 0.85 (95%CI, 0.75-0.97) in those with access to a cookstove. Exposure to CO was increased in females and current smokers and showed a seasonal trend.

We did not find evidence of accelerated lung function decline despite exposure to high levels of $PM_{2.5}$. Previous studies exploring the impact of $PM_{2.5}$ on lung function in high income settings have focused on $PM_{2.5}$ from ambient air pollution, particularly traffic-related air pollution. Faster lung function decline was associated with increasing $PM_{2.5}$ in longitudinal cohorts from the USA and Taiwan, the effects of other pollutants were not reported.[366,367] A large multi-centre metanalysis from the European ESCAPE cohorts did not find an association between air pollution and lung function decline but noted that NO_2 was negatively associated with lung function.[368] It is possible that the emissions from incomplete biomass combustion are less harmful to the airways than the many constituents (including nitrogen oxides) of traffic-related air pollution.

Previous work from Malawi has reported lung function relative to NHANES III Caucasian reference values, to facilitate comparison with other BOLD

studies.[22,23] In this analysis, we have additionally compared our data to African-American reference ranges (NHANES and GLI). The prevalence of reduced FVC varies greatly depending on which reference equation is used.[64] The prognostic significance of markedly different predicted values in different ethnic populations is unclear.[66] Reduced FVC is seen in restrictive lung disease, however more detailed assessment of total lung capacity by plethysmography is needed to further characterise the pattern of lung defect seen in African populations.

Use of GLI reference ranges permitted direct comparison with spirometry data from children living in the same community. We recently reported lung function for children aged 6-8 years, living in Chikhwawa; FEV_1, FVC and FEV_1/FVC ratio z-scores were -0.48 (0.93), -0.30 (0.96) and -0.38 (0.90), respectively, compared to GLI African American reference ranges.[365] The finding of similar z-scores in both the children and adults living in this community, suggests that factors which influence lung growth and development act in early childhood before 6 years of age, perhaps even starting *in-utero*.

We found an increase in self-reported respiratory symptoms over the 3-year follow-up period but no changes in exposures (self-reported TB or smoking status, or measured $PM_{2.5}$ or CO). We speculate this is due to changes in reporting behaviour rather than a true change in symptom prevalence. During the CAPS period, the local community were exposed to messages about the health impact of air pollution and may have become sensitized to the issues of clean air and respiratory health. Participants became familiar with the same questions asked on repeated occasions: this may have led a positive reporting bias. Alternatively, responses at baseline may have underreported symptom prevalence: a community survey in two rural districts in Central Malawi reported chronic respiratory symptoms in 22.5% of the population.[331]

Previous cookstove intervention trials have explored lung function in adult women only.[233,234] The RESPIRE randomised controlled trial in Guatemala, reported a reduction in 48-hour personal CO exposure in the intervention

group using a plancha woodstove but no effect on women's lung function at 12-18 months in an intention-to-treat analysis.[234] A subsequent exposure-response analysis did find a significantly decreased rate of decline with decreased exposure to CO.[235] Use of a Patsari stove in rural Mexico was associated with a significantly decreased rate of lung function (FEV_1) decline in women compared to those cooking on open fires (31ml vs 62ml), over one year of follow-up, but this effect was not observed on intention-to-treat analysis.[233] This decrease in decline is comparable to that reported among ex-smokers, in the first year after quitting; their FEV_1 trajectory showed half the rate of annual decline compared to those who continued to smoke ((mean ± SD) 31±48 vs 62±55ml).[223] Our finding of FEV_1 annual decline of 30.9ml is consistent with the ranges seen in non-smokers from various studies.[220]

Our findings would suggest that low lung volumes seen in Malawian adults are not a result of accelerated decline in lung function, but more likely a failure to reach maximal lung volumes in early adulthood, either due to low lung function at birth or suboptimal lung growth during early childhood. Low-birth weight and prematurity are of particular relevance in Malawi; the country has the highest rate of preterm birth worldwide, and intrauterine growth restriction, in both term and preterm infants, is common in low-income countries due to maternal factors including young maternal age, short-interpregnancy intervals and congenital infections.[152,153] Adverse effects of prenatal exposure to household air pollution on infant lung function has been suggested by the recent GRAPHS trial in Ghana.[40] The adverse effect of early respiratory infections on lung health in adulthood has long been recognised; such infections are common in sub-Saharan Africa, particularly during the first year of life.[129,369]

Several studies have used CO levels as a proxy for particulate matter, which is challenging to measure in the field in low-resource settings. However, respirable particulate matter ≤2.5µm ($PM_{2.5}$) can reach the alveolar level in the lungs and is of greater interest when considering adverse respiratory effects of air pollution. We found no association between $PM_{2.5}$, CO or access

to a cookstove and lung function. In keeping with findings from Peru, Nepal and Kenya, we observed poor correlation between CO and $PM_{2.5}$ measurements and different explanatory covariates for the two pollutants in our exposure models.[370] Although observed levels of exposure to both CO and $PM_{2.5}$ exceeded WHO upper safety limits, the duration of these high exposures was brief, and we speculate that adverse pulmonary effects are limited by the low intensity of exposure in rural Malawi where most cooking is done outdoors. Similarly, we found that current smoking was not associated with FEV_1 in this population, likely reflecting the low intensity of tobacco use among smokers in this community; less than one-fifth of current or ex-smokers at baseline reported cigarette consumption of greater than 10 pack years.

Strengths of our study include the collection of longitudinal lung function and personal air pollution exposure data in a rural cohort in one of the world's poorest countries; high quality spirometry performed by BOLD-certified technicians, with external quality control of traces by an independent expert reviewer. Limitations include potential recall bias and highly variable responses to questionnaires, and bias introduced by those not attempting spirometry or lost to follow-up. Participants performing spirometry were younger and hence it is likely that spirometric abnormalities, such as obstruction, which are associated with increasing age are likely to be underrepresented. Throughout the study the team struggled with cultural beliefs that older members of the community were "too weak" or "physically unable" to attempt spirometry. One third of participants from baseline were lost to follow-up by the end of the study; we were unable to ascertain the reasons for this due to limitations of the data collected, but comparison of the demographic data for those who remained in the study at each phase suggested that men and those with better education were more likely to be lost, reflecting the more economically active, mobile sector of society. We recognise that 3 years is a relatively short time period to track longitudinal changes in lung function but believe we would more likely observe any effect

of the intervention during the CAPS study period, when the use of the cookstoves was actively supported by a repair and maintenance programme. Given that the rate in decline in lung function we observed over 3 years was consistent with the rate of decline seen in healthy adults in Europe and North America it seems likely that this observation is accurate and that a longer period of follow up would not have yielded additional useful rate of decline information.

In conclusion, in our cohort of adults living in rural Malawi, we observed a) reduced FVC compared to Caucasian reference populations, similar in relative magnitude to what we previously reported in children living in the same communities, b) no evidence of accelerated decline in FEV_1 or FVC and c) no effect of access to cleaner-burning cookstoves on lung function decline. We suggest that future efforts to improve the lung health of those living in the poorest parts of the world should focus on antenatal and early childhood interventions to maximise lung growth and development. Further research is required to define the prognostic significance of reaching adulthood with suboptimal lung volumes, regardless of comparative reference range in terms of morbidity, mortality and associated socioeconomic costs.

5 Task-shifting to improve asthma management in children in Malawi: a randomised controlled trial

5.1 Introduction

Asthma is the most common chronic condition in childhood and is a growing concern in Africa.[20] Asthma causes an estimated 1000 deaths worldwide every day, and is a major cause of morbidity in children, ranking in the top ten causes of disability adjusted life years.[19,20] Asthmatic adults in sub-Saharan Africa (sSA) suffer frequent acute exacerbations, and have symptoms which are poorly controlled.[257,258,371] Limited data from asthmatic children living in sSA suggest higher rates of severe symptoms compared to high-income settings, likely due to challenges with diagnosis and quality of asthma care.[51]

The Malawi Standard Treatment Guidelines for asthma management are extrapolated from global guidelines, adopting a step-wise approach centred on inhaled corticosteroid (ICS) therapy.[372,44] These guidelines are appropriate where steroid-responsive, allergen-driven, eosinophilic asthma predominates: it is unknown whether this is true for Malawi. Limited evaluation of asthma guideline implementation in selected low- and middle-income countries (LMICs), found that physicians often underutilise ICS treatment, and that patient adherence to treatment is a challenge.[306,307] Reasons for poor adherence are likely to be multifactorial, including unreliable supplies of affordable medication, and misconceptions regarding effective asthma treatments.[308,310]

Asthma education and the use of an Asthma Action Plan (AAP) are considered important elements of chronic asthma management in high-income countries (HIC) and are recommended in international guidelines.[44] Studies demonstrating a beneficial impact of asthma education in HIC include a wide range of interventions, with variable content, duration and delivery methods.[313,315] AAPs facilitate the early detection and treatment of an exacerbation, and have been shown to improve asthma health outcomes in

HIC.[319] However, the provision of asthma education can be time consuming and human resources constraints in Malawi limit the quality of care available. Task shifting, defined as "the transfer of a task normally performed by a more highly trained health care worker to another with a different, usually lower level of training," is a possible solution, but research exploring this approach to asthma management in LIC is lacking.[336,348]

We implemented a package of enhanced asthma care, appropriate for a LIC, which included a standardised clinical assessment, optimisation of locally available inhaled asthma treatment, and asthma education delivered by non-clinical staff.

We aimed to assess the feasibility of the intervention and describe baseline levels of asthma control and exacerbation rates in asthmatic children living in urban Blantyre, Malawi. Furthermore, we planned to; evaluate the effect of a package of enhanced asthma care over a 3-month period; to describe clinical and airway inflammatory phenotypes; to identify clinical features which might predict response to treatment, in this population.

5.2 Methods

5.2.1 Setting

Queen Elizabeth Central Hospital (QECH), a government-run, tertiary hospital, located in Blantyre, Malawi's second largest city, receives referrals from throughout the Southern Region. Children attending the general paediatric clinic are referred from primary health centres, and from within QECH following emergency department attendance or ward admission.

5.2.2 Trial design

We did a non-blinded, individually randomised controlled trial comparing the effects of an enhanced asthma care package with standard outpatient care at QECH.

5.2.3 Participants

All children aged 6-15 years attending the general paediatric outpatient clinic at QECH with a doctor-diagnosis of asthma recorded in their health passport were invited to participate in the study. Children with symptoms suggestive of tuberculosis were excluded; productive cough, haemoptysis, weight loss, recurrent fevers or night sweats. Study visits were postponed if children were acutely unwell, or had a respiratory infection, asthma exacerbation or received oral corticosteroids in the previous 4-weeks.

5.2.4 Consent and randomisation procedure

Study information was provided in the local language (Chichewa). Following written informed consent from the parent or guardian and assent from the child, a baseline electronic questionnaire was completed; children were stratified according to their level of asthma control, as assessed by the childhood Asthma Control Test (cACT), into two groups (cACT≥20 or cACT≤19).[259] Within each group, individuals were allocated 1:1 to intervention or standard care arms using pre-generated variable length, permuted block randomisation codes. Allocation information was not accessible to any staff prior to electronic questionnaire completion.

5.2.5 Study procedures

The intervention comprised 3 components; detailed clinical assessment, optimisation of locally available inhaled asthma treatment, and asthma education delivered by non-clinical staff.

5.2.5.1 *Intervention: Clinical assessment*

Participants in the intervention arm attended the hospital shortly after recruitment for an assessment visit at which clinical examination, anthropometry, exhaled nitric oxide (FeNO) measurement, pre-and post-bronchodilator spirometry, and exercise challenge were done. All study procedures were performed according to standardised operating procedures, with regular quality control monitoring by the study clinician. Asthma symptoms were assessed using Global Initiative for Asthma (GINA) and International Study of Asthma and Allergies in Childhood (ISAAC)

questionnaires.[44,51] Spirometry was conducted by experienced technicians, using an Easy On-PC spirometer (ndd Medical Technologies), according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[58] Lung function was measured before and after 400µg salbutamol administered by metered-dose inhaler via a Volumatic spacer. Lung function parameters; forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio and bronchodilator responsiveness, were interpreted with reference to the African American Global Lung Initiative 2012 equations.[57]

Carboxyhaemoglobin (COHb) was measured non-invasively using a Rad-57 Pulse CO-Oximeter (Masimo Corporation). FeNO was measure using an NObreath machine (Bedford Scientific Ltd.), following ATS/ERS guidelines.[373] Provided their FEV_1 was >75% predicted value, participants underwent exercise challenge, running at maximum effort for 6-minutes with FEV_1 monitored at five- and ten-minutes post-exercise.

5.2.5.2 *Intervention: Optimisation of inhaled asthma treatment*

Following the clinical assessment, ICS treatment was started or escalated to a maximum daily dose of 400µg of beclometasone dipropionate, for children with poor control or obstructive spirometry (as indicated by cACT≤19 or FEV_1/FVC ratio below the lower limit of normal (LLN) respectively). These participants were reviewed after 6-weeks to assess their response and to encourage treatment adherence. Participants with cACT≥20 and FEV_1/FVC above the LLN continued their previous medication.

5.2.5.3 *Intervention: Asthma education delivered lay educators*

Non-clinical "lay educators" delivered a 1-hour asthma education session to the child and carer, including discussion of a personalised AAP (Figure 5-1), with oversight by the study clinician or nurse. Before study initiation, educators completed a structured training programme (Table 5-1) and were required to pass a formal assessment of their knowledge and skills. Each asthma education session followed a structured approach, with checklist, to ensure consistency within and between educators (Table 5-2).

Pre-study training programme

Before the study started, four "lay educators" received training by the study doctor. These staff had completed secondary school, with a Malawi School Certificate of Education, but had no previous medical experience or training. The lay educators spent time with the study doctor in the paediatric clinic to gain experience with asthma patients and their families. Formal training comprised four hour-long tutorials (Table 5-1), with an accompanying training manual for self-study, after which the educators were required to gain at least 80% in a knowledge test (comprising 20 true/false questions) and demonstrate competence at delivering the asthma education session in a role-play session. The educators were supported by the study medical staff and encouraged to seek advice throughout the study period.

Table 5-1. Pre-study asthma training for lay educators

Session	**Key content**
1) What is asthma?	Chronic inflammation of airways and airway narrowing
	Recurrent symptoms; cough, wheeze, difficulty breathing
	Impact of poor asthma control, including death with severe attack
	Symptoms can be well controlled with inhaled treatment
	Common triggers for asthma symptoms
2) Asthma treatment	Types of inhaler: relievers (β_2 agonist) and preventers (steroid)
	Use of a spacer to improve drug delivery
	Importance of long-term adherence
3) Self-management	Monitoring of symptoms
	What to do in an asthma attack
	Asthma Action Plans
4) Practical session	Inhaler technique – how to demonstrate
	How to deliver an asthma education session

Education session content

Study participants received a 1-hour individualised asthma education session, delivered to the child and their carer by lay educators, with oversight by the study doctor or nurse. A structured approach, with checklist (**Error! Reference source not found.**Table 5-2), was followed to ensure intra- and inter-educator consistency. Education sessions were conducted in Chichewa, and patients received a written asthma action plan, also in Chichewa (Figure 5-1).

Table 5-2. Asthma education checklist

	Please tick
General approach	
Establish good rapport with child and family	
Establish what is known already about asthma, treatments etc.	
Explore beliefs, fears and concerns (cause of asthma, effect of medications)	
Content	
What is asthma?	
What symptoms does asthma cause?	
Rationale for treatment – differences between “relievers” and “controllers”	
Encourage adherence, even when control is good	
Inhaler/spacer skills training	
• Including demonstration of inhaler/spacer technique by fieldworker	
• Observe participant’s technique	
Discuss possible triggers and avoidance	
How to recognise worsening symptoms and what to do	
Discuss and provide written asthma action plan	
Arrange next medical review	
Answer any questions	

Ndondomeko Yanga ya Mphumu

Dzina: .....

Tsiku lobadwa: ...../...../.....

Dzina la chipatala: .....

1 Mankhwala anga a mphumu

Mankhwala anga oteteza mphumu amatchedwa ***Beclomethasone*** (maonekedwe ake a ***brown***)

Ndimatenga mapafu___mammawa ndi mapafu___usiku.
Ndimachita izi tsiku lililonse ngankhale ndili bwino.

Mankhwala anga oletsa kubanika amatchedwa ***Salbutamol*** (wa maonekedwe ake a ***blue / yellow***)

Ndimatenga mapafu___pamene ndi kukhosomola kapena kuliza makwiyo, komanso ndi kubanika.

Ndimayenera kugwiritsa ntchito botolo lothandizira pogwiritsa ntchito mankhwala.

2 Pamene mphumu yanga yavutitsa

Ndizadziwa pamene mphumu yanga ikufika povuta ngati:

- Ndikukhosomola, kuliza makwiyo kapenanso ndikuvutika kupuma.
- Ndimadzuka usiku chifukwa cha zizindikiro zanga.
- Ndimayenera kugwiritsa ntchito mankwala oletsa kubanika katatu pa sabata.
- Ndimayeneranso kutenga mapafu anayi a mankhwala oletsa kubanika pa maola anayi aliwonse.

Zimayambitsa mphumu yanga:

3 Ndikabanika ndi mphumu

Ndimabanikabe ngati:

- Mankhwala anga oletsa kubanika sakuthandiza
- Sindikutha kuyankhula kapena kuyenda bwinobwino
- Ndikukhosomola kapena kuliza makwiyo kwambiri

Ndiyenera kuti:

- Ndikhale pansi tsonga ndikuyetsa kudekha.
- Nditenge pafu imodzi ya mankhwala anga oletsa kubanika pa mphindi iliyonse mpaka akwane mapafu khumi.

Ngati sindikupezabe bwino:

- Ndiyenera ndipite ku chipatala nthawi yomweyo.
- Nditha kutenganso mapafu ena khumi pamane ndikupita ku chipatala.

Figure 5-1. Asthma Action Plan

Patients with poor control (cACT≤19) or airway obstruction (FEV_1/FVC below lower limit of normal) at the time of the first education session, attended a further session at 6-weeks to check understanding and encourage adherence.

5.2.5.4 *Standard care*

Participants in standard care continued with their asthma treatment and follow-up schedule as prescribed by the QECH clinic staff (paediatric specialist of registrar or consultant level).

All study participants received their medication from the QECH pharmacy: salbutamol and beclometasone dipropionate inhalers are included in the Malawi Standard Treatment Guidelines, and usually available, free of charge. At times when inhalers were out of stock, children received their inhalers from a private supply, purchased by the Paediatric department to prevent treatment interruptions.

5.2.6 Outcomes

All participants were invited to attend a study review at 3-months for assessment of primary and secondary outcomes. The primary outcome, asthma symptom control, was measured by the cACT, a 7-item questionnaire, translated into Chichewa according to linguistic validation guidelines.[374] Secondary outcomes were asthma exacerbations requiring hospitalization, emergency health care use or treatment with oral corticosteroid; school absence; lung function; FeNO. Serious adverse events were reported within 72-hours to a Data Safety and Monitoring Board, which also met at regular intervals.

5.2.7 Follow-on care

At the end of the 3-month study period, those in the intervention arm returned to care in the general clinic. Participants in the standard care arm were invited to attend an assessment visit, including the asthma education intervention and were reviewed again after 3-months, with a questionnaire and FeNO and spirometry assessment.

5.2.8 Sample size

We planned to enrol 120 participants, aiming for a sample of at least 90 children with complete data, after loss-to-follow-up and technical difficulty with clinical procedures. Using two-tailed Student's t-test, 45 children in each

arm will detect a difference in cACT of 3 points; an effect size of 0.6, given standard deviation 5, with 80% power at a 5% significance level.

5.2.9 Statistical methods

Intention-to-treat analysis compared primary and secondary outcomes between the intervention and standard care arms using two-tailed Student's t-test and Wilcoxon Signed-Rank test for normally distributed and non-parametric continuous data, respectively. Pearson's Chi-squared tests were used to compare proportions. Pearson and Spearman correlation coefficients were calculated to explore associations between parametric and non-parametric continuous variables, respectively. Predictors of change in cACT over 3-months were explored in a multivariable linear regression model, using a backward stepwise regression technique, including variables with a p-value <0.2 on bivariate analysis. Analyses were conducted using R version 3.4.1 statistical software.

5.2.10 Approvals and registration

The study was approved by the College of Medicine, Malawi (reference P.04/18/2384) and Liverpool School of Tropical Medicine, UK (reference 18-018) Research Ethics Committees. The trial was registered with the Pan African Clinical Trials Registry (reference PACTR201807211617031).

5.3 Results

We recruited 120 children between September 2018 and December 2019; 59 were randomised to receive enhanced care, and 61 to receive standard care. Mean age (SD) of participants was 9.8 (2.8) years with 65.8% males. 115 participants attended for review at 3-months, with data collected as shown in Figure 5-2. Mean (SD) duration of follow-up, to RCT completion, was 96.6 (12.0) days and 91.0 (10.1) days for enhanced and standard care participants, respectively. Following completion of the initial 3-month follow-up, 58 participants from standard care attended for assessment, asthma education and optimisation of treatment, with 48 reviewed after another 3-months (Figure 5-3).

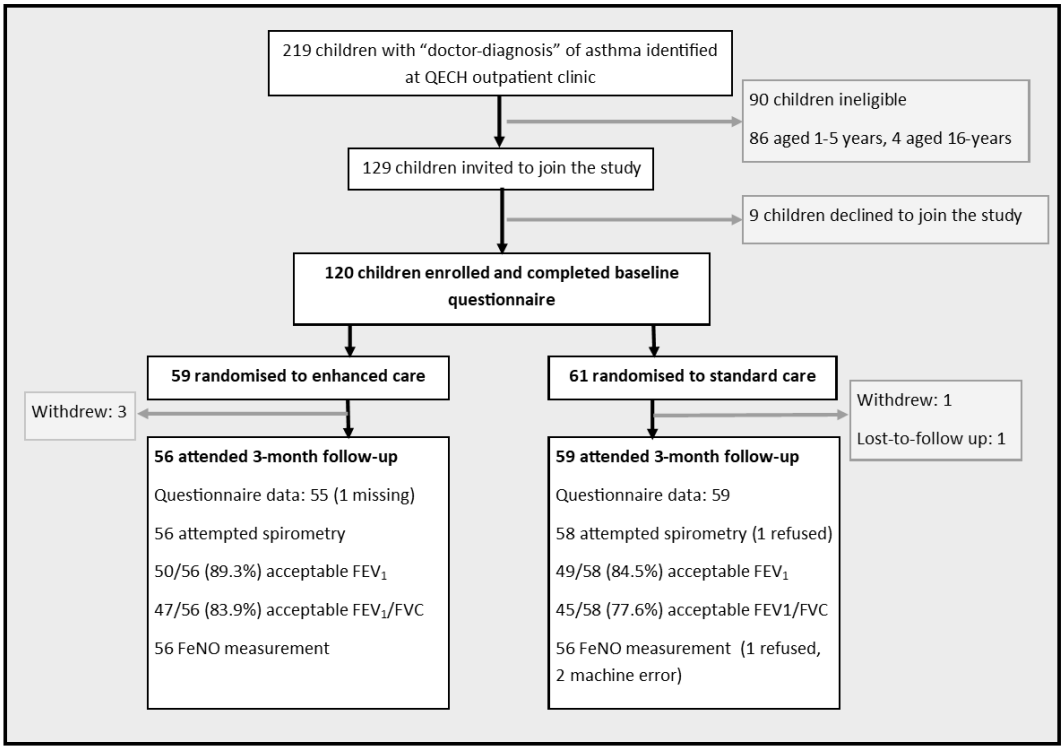


Figure 5-2. Participant recruitment and follow-up for the RCT analysis

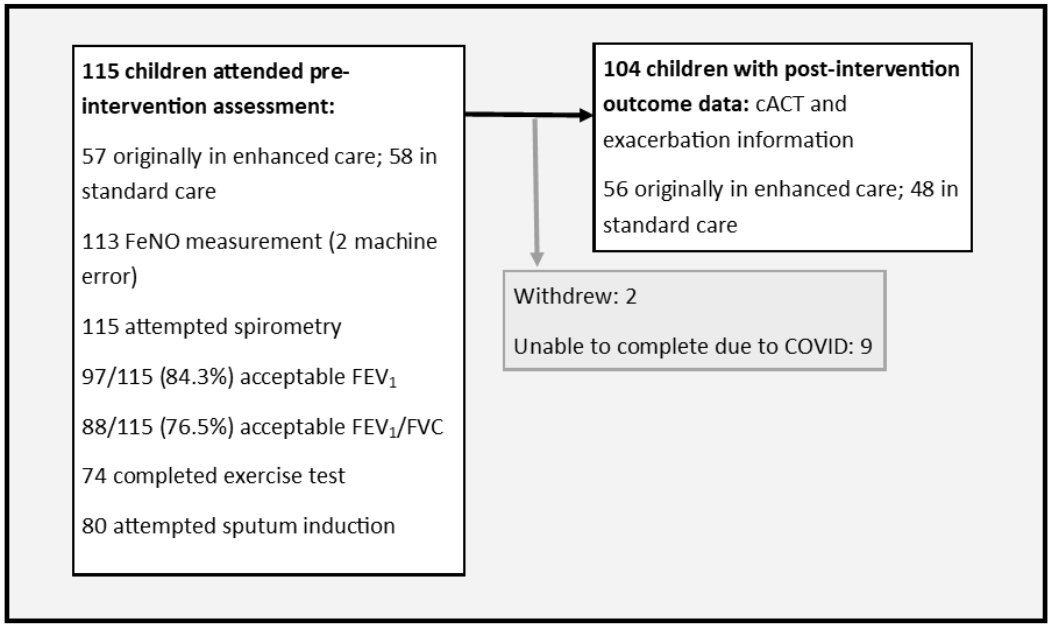


Figure 5-3. Data collected for participants before and after the enhanced care intervention

5.3.1 Asthma symptoms and treatment at enrolment

Eighty percent of participants reported previous hospital admission with asthma symptoms. In the preceding 3-months, 28/120 (23.3%) were admitted to hospital, 39/120 (32.5%) attended a health facility, but did not require admission, and 79/120 (65.8%) missed school due to asthma symptoms. Median (IQR) school absence was 3 (2-5) days, with 58.2% (46/79) of absentees seeking medical review. Baseline clinical characteristics were similar for both study arms (Table 5-3).

Table 5-3. Baseline characteristics of study population (n=120)

	Enhanced care n=59	**Standard care n=61**
Age, mean (SD) years	10.1 (2.8)	9.4 (2.9)
Sex: female, n (%)	18 (30.5)	23 (37.7)
Hospital admission ever, n (%)	47 (79.7)	49 (80.3)
Hospital admission in past 3 months, n (%)	14 (23.7)	14 (23.0)
Health facility attendance in past 3 months, n (%)	18 (30.5)	21 (34.4)
School absence in past 3 months, n (%)	40 (67.8)	39 (63.9)
School absence in past 3 months, median days (IQR)	3 (2-5)	3 (2-5)
Reported using salbutamol inhaler	45 (76.3)	51 (83.6)
Reported using steroid inhaler regularly	21 (35.6)	28 (45.9)
Daily dose beclometasone	238 µg (n=21)	273 µg (n=28)
GINA: Well controlled (score* 0)	12 (20.3)	7 (11.5)
GINA: Partly controlled (score* 1-2)	20 (33.9)	21 (34.4)
GINA: Uncontrolled (score* 3-4)	27 (45.8)	33 (54.1)
cACT, mean (SD)	20.4 (2.9)	20.3 (2.3)
cACT ≥20 (well controlled)	37 (62.7)	40 (65.6)
cACT ≤19 (poor control)	22 (37.3)	21 (34.4)
Pre-bronchodilator lung function		
Mean (SD) % predicted FEV_1 [†]	88.1 (18.4)	-
Mean (SD) % predicted FEV_1/FVC ratio[‡]	89.0 (10.0)	-
FEV_1/FVC ratio below LLN, no. children (%)[‡]	17/43 (39.5)	-
Fractional concentration of exhaled nitric oxide (FeNO)		
Median (IQR) FeNO, ppb[#]	44.5 (27.5-66.5)	-
High (>35 ppb), no. children (%)	34 (59.6)	-
Intermediate (20-35 ppb), no. children (%)	15 (26.3)	-
Low (<20 ppb), no. children (%)	8 (14.0)	-

* Score 1 for each positive response to: In the past 4-weeks, has the patient had: a) Daytime asthma symptoms more than twice/week? b) Any night waking due to

asthma? c) Reliever needed for symptoms more than twice/week? d) Any activity limitation due to asthma?
[†]Technically acceptable FEV_1 data available for 48 participants at baseline
[‡]Technically acceptable FEV_1/FVC data available for 43 participants at baseline
[#]FeNO available for 57 participants at baseline

Most children (106/120, 88.3%) reported wheezing in the past year; overall 68.3% (82/120) experienced ISAAC-defined severe asthma symptoms, with at least one of; ≥4 attacks (64/106, 60.4%), wheeze-related sleep disturbance more than once per week (34/106, 32.1%), or wheeze affecting speech (38/106, 35.8%), in the past year. By GINA criteria, asthma symptoms were well controlled in 19 (15.8%), partly controlled in one third (41/120) and uncontrolled in half (60/120) of participants. The baseline mean (SD) cACT score was 20.3 (2.6), with 43 (35.8%) participants stratified as having poor control (cACT≤19) and 77 (64.2%) with good control (cACT≥20). Responses to individual cACT questions are shown in Table 5-4.

At enrolment 96/120 (80.0%) participants reported using a salbutamol inhaler, with 67/96 (69.8%) using a spacer; 41/120 (34.1%) participants reported using a beclometasone inhaler (+ spacer) regularly, with a mean daily dose of 258µg and self-reported adherence of 89.6%.

None of the participants had been previously treated for tuberculosis. Of 105 participants who had been tested for HIV, all were HIV-negative. Half of participants (62/120, 51.7%) reported a family history of asthma, including 47/120 (39.2%) with asthma in a first-degree relative. The majority of participants experienced wheezing in early childhood; 52/120 (43.3%) reported wheeze onset before age 3 years, 41/120 (34.2%) aged 3-6 years, and 27/120 (22.5%) after age 6 years. Atopic symptoms were common; with self-reported rhinitis, hay fever, and eczema in 72/120 (60.0%), 37/120 (30.8%) and 31/120 (25.8%), respectively.

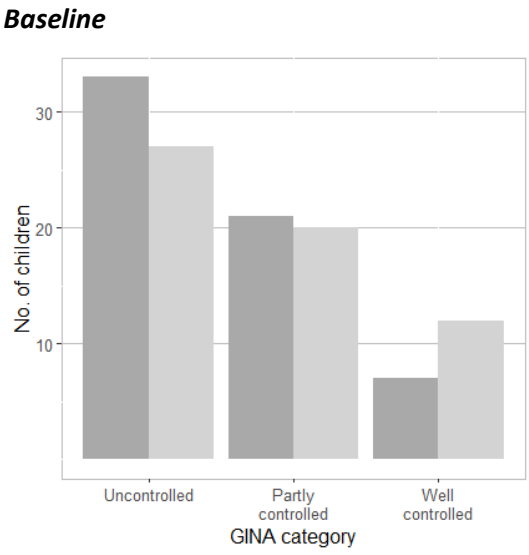
Table 5-4. Baseline responses to cACT questionnaire from participants and carers.

	Question	Score	Responses n (%)
Child	How is your asthma today?	0 (very bad)	1 (0.8)
		1 (bad)	8 (6.7)
		2 (good)	58 (48.3)
		3 (very good)	53 (44.2)
	How much of a problem is your asthma when you run, exercise or play sports?	0 (it's a big problem)	7 (5.8)
		1 (it's a problem and I don't like it)	24 (20.0)
		2 (it's a little problem but it's OK)	71 (59.2)
		3 (it's not a problem)	18 (15.0)
	Do you cough because of your asthma?	0 (yes, all the time)	3 (2.5)
		1 (yes, most of the time)	15 (12.5)
		2 (yes, some of the time)	102 (85.0)
		3 (no, none of the time)	0
	Do you wake up during the night because of your asthma?	0 (yes, all the time)	0
		1 (yes, most of the time)	10 (8.3)
		2 (yes, some of the time)	90 (75.0)
		3 (no, none of the time)	20 (16.7)
Carer	During the last 4-weeks, how many days did your child have any daytime asthma symptoms?	0 (everyday)	0
		1 (19-24 days)	0
		2 (11-18 days)	4 (3.3)
		3 (4-10 days)	28 (23.3)
		4 (1-3 days)	69 (57.5)
		5 (not at all)	19 (15.8)
	During the last 4-weeks, how many days did your child wheeze during the day because of asthma?	0 (everyday)	0
		1 (19-24 days)	0
		2 (11-18 days)	1 (0.8)
		3 (4-10 days)	18 (15.0)
		4 (1-3 days)	42 (35.0)
		5 (not at all)	59 (49.2)
	During the last 4-weeks how many days did your child wake up during the night because of asthma?	0 (everyday)	0
		1 (19-24 days)	0
		2 (11-18 days)	4 (3.3)
		3 (4-10 days)	16 (13.3)
		4 (1-3 days)	53 (44.2)
		5 (not at all)	47 (39.2)

5.3.2 Clinical outcomes at 3-month follow-up

At 3-months, children in the intervention arm had a mean (SD) cACT of 22.9 (2.3), compared to 20.8 (3.0) in standard care ($p<0.001$). Children receiving

the intervention had a greater mean (SD) change in cACT score from baseline; 2.7 (2.8), compared to 0.6 (2.8) for standard care participants, a difference of 2.1 points (95% CI: 1.1-3.1) (p<0.001) – see Table 5-5. Participants receiving enhanced care reported improvement in symptoms and GINA score, with little change for those receiving standard care (Figure 5-4 and Figure 5-5).



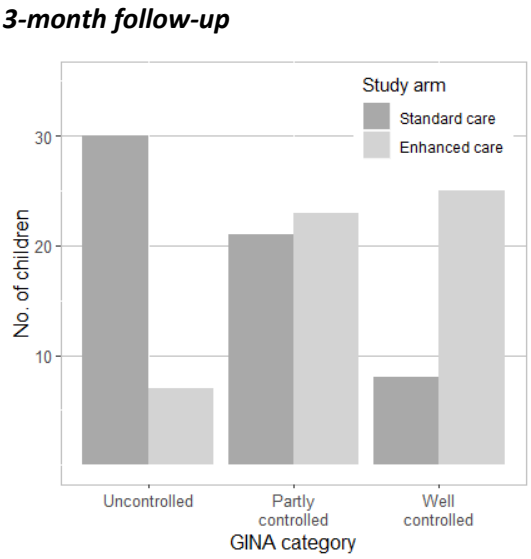


Figure 5-4. *(left)* Comparison of GINA categories at baseline (n=120)
Figure 5-5. *(right)* Comparison of GINA categories at 3-month follow-up (n=114)
Standard care is shown in dark grey and enhanced care in light grey.

Hospital admission and health facility attendance fell in both arms, compared to baseline. Compared with standard care, the enhanced care arm reported lower rates of admission (3.6% vs 10.2%, p=0.32), overall emergency health facility attendance (7.3% vs 25.4%, p=0.02), and school absence (20.0% vs 62.7%, p<0.001) (Table 5-5). Oral prednisolone was given during 8/30 (26.7%) exacerbations requiring emergency health care use.

FeNO levels and spirometry results were similar for both study arms at 3-months (Table 5-5). There were no significant differences in age, sex, study arm and baseline cACT between those with and without spirometry results (Table 5-6).

Table 5-5. Asthma outcomes at 3-months for 114 participants.

	Enhanced care n=55	Standard care n=59	Comparison
Primary outcome: cACT score			
cACT score, mean (SD)	22.9 (2.3)	20.8 (3.0)	P<0.001
Change in cACT score from baseline, mean (SD)	2.7 (2.8)	0.6 (2.8)	P<0.001
Secondary outcomes			
Health care use			
Exacerbations with hospitalization, no. children (%)	2 (3.6)	6 (10.2)	P=0.32
Exacerbations with health facility attendance but not admission, no. children (%)	3 (5.5)	11 (18.6)	P=0.06
Exacerbations with any emergency health care use, no. children (%)	4 (7.3)	15 (25.4)	P=0.019
School absence			
School absence, no. children (%)	11 (20.0)	37 (62.7)	P<0.001
Pre-bronchodilator lung function			
Mean (SD) % predicted FEV_1 †	86.9 (18.0)	92.0 (17.5)	P=0.15
Mean (SD) % predicted FEV_1/FVC ratio‡	90.9 (12.5)	92.8 (10.3)	P=0.42
FEV_1/FVC ratio below LLN, no. children (%)‡	15/47 (31.9)	13/45 (28.9)	P=0.93
Fractional concentration of exhaled nitric oxide (FeNO)			
Median (IQR) FeNO, ppb *	41.8 (23.4-68.0)	39.8 (22.9-57.9)	P=0.64
High (>35 ppb), no. children (%)	33 (58.9)	31 (55.4)	P=0.85
Intermediate (20-35 ppb), no. children (%)	11 (19.6)	15 (26.8)	P=0.50
Low (<20 ppb), no. children (%)	12 (21.4)	10 (17.9)	P=0.81

†Technically acceptable FEV_1 data available for 99 participants

‡Technically acceptable FEV_1/FVC data available for 92 participants

* FeNO data available for 112 participants

Table 5-6. Comparison of those with and without spirometry data at 3-month follow-up

	With spirometry data n=99	Without spirometry data n=15	Bivariate analysis
Age, mean (SD) years	9.7 (2.7)	9.2 (3.3)	p=0.56†
Sex: female, n (%)	35 (35.4)	3 (20.0)	p=0.38‡
Baseline ACT, mean (SD)	20.3 (2.6)	19.7 (2.5)	p=0.43†
Study arm: intervention, n (%)	50 (50.5)	6 (40.0)	p=0.63‡

†Student's t-test for continuous data, ‡Pearson's χ^2 for categorical data

5.3.3 Asthma treatment at 3-month follow-up

At 3-months, 98.1% (54/55) children in enhanced care were using a salbutamol inhaler with a spacer compared to 83.1% (49/59) in standard care. Daily ICS use was more common in enhanced care (47/55, 85.5% participants) compared to standard care (41/59, 69.5% participants), with enhanced care participants prescribed a higher mean (SD) daily beclometasone dose: 331µg (121) vs 266 µg (99). Self-reported adherence was 85.4% and 85.5% among enhanced and standard care participants, respectively. Four carers (3 from enhanced care, 1 from standard care) reported non-availability of inhalers at QECH during the trial period.

5.3.4 Clinical predictors of response to "enhanced care" intervention

Overall, 115 participants were assessed before receiving the enhanced care package, with post-intervention outcome data collected for 104 participants. Mean (SD) percentage of predicted FEV_1 was 90.1 (17.9) and mean percentage predicted FEV_1/FVC ratio 91.0 (10.3), with one-third (30/88, 34.1%) of participants having a FEV_1/FVC ratio below the lower limit of normal. Thirteen participants had FEV_1/FVC<0.7, of which five had cACT ≥23. The distribution of lung function parameters is shown in Figures 5-6 and 5-7.

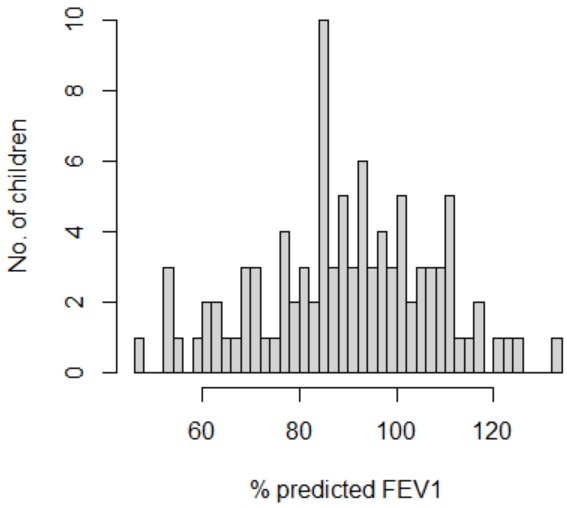


Figure 5-6. Distribution of percentage predicted FEV1 measurements (n=97)

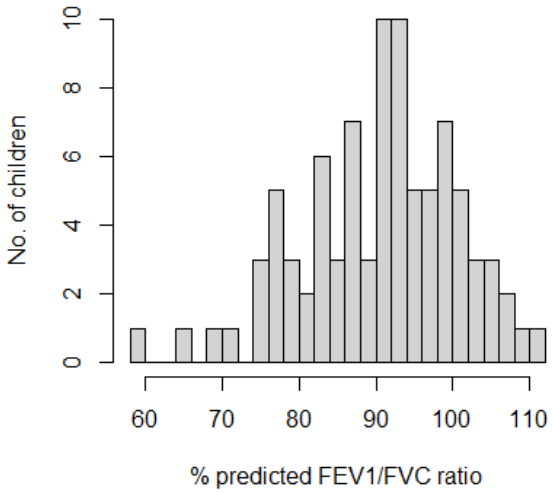


Figure 5-7. Distribution of percentage predicted FEV_1/FVC ratio (n=88)

Of participants with baseline FEV_1>75%, eligible for exercise challenge, half (37/74, 50.0%) had an FEV_1 fall of >12% predicted. Post-bronchodilation, 45/115 (39.1%) participants showed an improvement in FEV_1 >12% predicted and overall 54.6% (53/97) participants demonstrated variability in FEV_1 of >12% during the visit. FeNO levels were high, with a median (IQR) of 41.5 (25.0-63.0) ppb and over half of participants (65/113, 57.5%) with a FeNO >35 ppb (Figure 5-8).

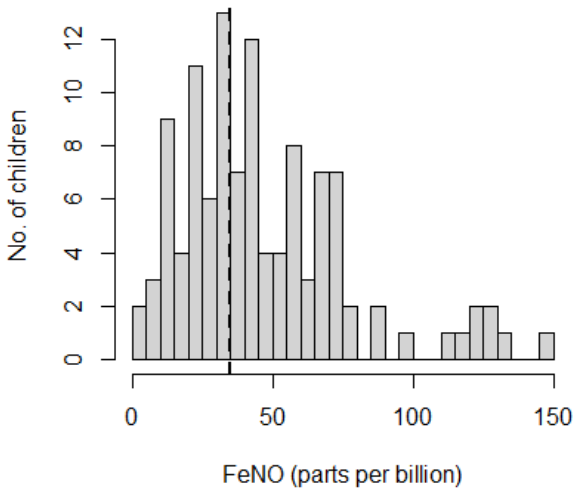
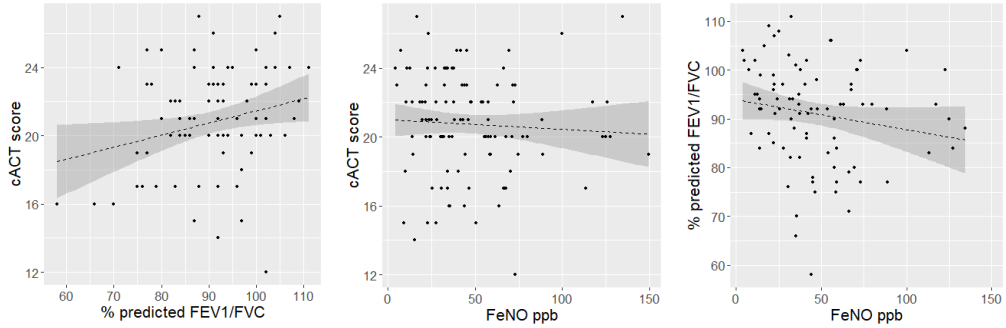


Figure 5-8. Distribution of FeNO levels measured pre-intervention (n=113)
Dashed line shows threshold for high FeNO (>35ppb)

Median carboxyhaemoglobin was 3.5% (IQR 1.5-6.5) and this was not associated with cACT score or FEV_1/FVC on bivariate analysis.

The correlation between clinical measurements was weak, with correlation coefficients of 0.24, -0.15 and -0.26 for cACT and FEV_1/FVC ratio, cACT and FeNO level, and FEV_1/FVC ratio and FeNO level, respectively – see Figures 5-9, 5-10 and 5-11.



Pearson coefficient 0.24, p=0.026

Spearman coefficient -0.15, p=0.13

Spearman coefficient -0.26, p=0.01

Figure 5-9. *(left)* Correlation between percentage predicted FEV_1/FVC and cACT score (n=88)

Figure 5-10. *(centre)* Correlation between FeNO level and cACT score (n=113)

Figure 5-11. *(right)* Correlation between FeNO level and percentage predicted FEV_1/FVC (n=86)

On bivariate analysis, age of wheeze onset, pre-intervention cACT score, FeNO level and FEV_1/FVC ratio, showed potential association ($p<0.2$) with a greater change in cACT over the 3-month intervention period and were explored in a multivariable linear regression model (Table 5-7). On multivariable analysis, lower pre-intervention cACT score and FEV_1/FVC ratio were both significantly associated with a greater response to the intervention (Table 5-7), other variables were dropped from the model.

Table 5-7. Predictors of response to intervention: change in cACT score.

	Bivariate linear regression		**Multivariable linear regression**	
Covariate	Coefficient estimate (95% CI)	p-value	Coefficient estimate (95% CI)	p-value
Age	0.09 (-0.13 - 0.32)	0.42	-	
Sex (male)	-0.47 (-1.80 – 0.85)	0.49	-	
Age of wheeze onset 3-6 years	1.04 (-0.39 – 2.47)	0.16	-	
Age of wheeze onset >6 years	1.49 (-0.11 – 3.09)	0.07	-	
Positive family history of asthma	-0.18 (-1.47 – 1.11)	0.78	-	
ICS naive	-0.39 (-0.39 to 0.67)	0.56	-	
Pre-intervention measurements				
cACT score	-0.70 (-0.89 - -0.53)	<0.001	-0.56 (-0.74 - -0.38)	<0.001
FeNO level, ppb	0.02 (-0.01 – 0.04)	0.16	-	
FEV_1/FVC ratio % predicted	-0.08 (-0.16 - -0.01)	0.03	-0.07 (-0.13 - -0.02)	0.008

In the 3-months following the education intervention, 9/104 (8.7%) participants attended a health facility with an asthma attack on a total of 15 occasions, including four hospital admissions. The clinical details of these nine participants are included in Table 5-8. There were no clinical features significantly associated with emergency health care use on bivariate logistic regression, although the study was not powered to this outcome.

Table 5-8. Clinical information for participants with emergency health care attendance during the following 3-month period (n=9)

ID	*Admission*	*Attendance (no admission)*	*Age (years)*	*Sex*	*ACT*	*FeNO (ppb)*	*FEV_1/FVC % predicted*	*Daily dose beclometasone (µg)*
P136	1	2	13	M	21	34	84	400
G457	1	0	8	M	22	54	92	0
G453	0	1	9	M	21	24	-	400
P108	0	2	6	F	17	34	88	200
G416	1	1	10	M	23	72	100	200
P104	1	1	7	F	14	15	92	200
G415	0	1	9	M	22	58	90	0
P130	0	1	6	F	15	23	97	400
G460	0	2	7	M	22	28	-	200

5.3.5 Adverse events

During the study period, six participants (3 from each arm) reported hospital admission for exacerbation of asthma. There were no other adverse events.

5.4 Discussion

To our knowledge, this is the first randomized controlled trial of a task-shifting intervention using non-medically trained asthma educators on asthma outcomes in sSA. The key finding was a clinically and statistically significant improvement in asthma control in the intervention vs standard care group (increase in mean (SD) cACT score of 2.7 (2.8) vs 0.6 (2.8) points, p<0.001)). We found a high burden of symptoms among asthmatic children attending an outpatient clinic at baseline; in the preceding 3-months, one-quarter of participants had been admitted to hospital, a further one-third had attended a health facility, without overnight admission, and two-thirds had missed school due to acute asthma symptoms. The overall mean (SD) cACT was 20.3 (2.6), with 85% of participants reporting sub optimal asthma control, by GINA criteria. Despite a high burden of symptoms and previous engagement with

the health care system, one fifth had no salbutamol inhaler, and less than half had received ICS treatment, with relatively low mean daily doses.

In addition to improved asthma control, fewer children in the enhanced care group experienced asthma exacerbations requiring emergency health facility attendance (7.3% vs 23.7%, p=0.03), and school absence (20.0 vs 61.0%, p<0.001). There were also fewer hospital admissions among enhanced care patients, although the admission rates in both groups were too small to detect a significant reduction.

Participants demonstrated raised FeNO levels, confirming that ICS treatment is highly appropriate in this population. Self-reported ICS use was greater in the enhanced care group, with more children taking daily beclometasone, and participants prescribed a significantly higher daily dose. Despite apparently greater ICS use, there was no difference in median FeNO levels at 3-months, suggesting unchanged levels of airway inflammation. Self-reported adherence rates were high (>85%), however adherence rates are frequently below 50% when steroid inhaler use is assessed objectively in HIC: low ICS adherence would explain the unaltered levels of inflammation in our participants.[375]

Improved outcomes maybe due to increased confidence to intervene early in an attack, with self-management of symptoms at home, using inhaled Salbutamol. Participants were generally able to collect inhalers, free of charge, from the hospital pharmacy, however inhaled treatment has very limited availability outside of tertiary health facilities in Malawi.

Lower pre-intervention cACT and decreased FEV_1/FVC ratio were associated with a greater response to the intervention which may represent the greater potential for improvement from baseline in children with more severe initial symptoms. However, our findings suggest that spirometry was a useful additional assessment tool. We identified several children with severe airway obstruction but normal cACT scores; symptom perception may be impaired in children with chronic airflow obstruction and the poor correlation between self-reported symptoms and spirometry is well-recognised.[267,268] Spirometry is unlikely to be available outside of the research setting in most LMIC, but peak flow meters can provide a useful alternative and may be a more appropriate

component of future interventions.[44] We did not include peak expiratory flow rate (PEFR) monitoring in the individual management plans as peak flow meters are not currently available in QECH: further research to explore the feasibility and effectiveness of this approach in LMICs is needed.

We found relatively high levels of reported asthma control (64.2%), defined by cACT≥19, compared to other studies in sSA, although most published data relate to adult patients. Among Ugandan patients, aged 5-93 years, attending tertiary care, only one third had controlled asthma (ACT>19), and exacerbation rates were high (59.6% patients had one exacerbation and 33.4% had 3 or more, during one year of follow-up).[371] In a teaching hospital respiratory clinic in Nigeria, 43.4% of adult patients had good control (ACT≥20).[257] Among paediatric patients attending a tertiary clinic in Johannesburg, South Africa, 55.7% had controlled asthma (ACT/cACT >19).[263] However, despite the baseline cACT for our participants suggesting reasonable control of asthma symptoms, the burden of exacerbations requiring health facility attendance and school absence was high.

In the absence of a locally validated assessment tool, the choice of outcome measurement for this study was challenging. The cACT is validated for use with children aged 4-11 years; with four questions for the child and three for their accompanying adult.[259] It has been used, although not validated, in South Africa: mean (SD) cACT score was 19.9 (5.5) for asthmatic children attending a tertiary hospital clinic in Johannesburg.[263] We chose to use the cACT for all participants, rather than separate tools for children 4-11 years and ≥12 years, for logistical reasons, and to collect complementary information from both the child and their caregiver. However, there are challenges to obtaining responses which truly reflect the child's clinical condition; younger children may have difficulty recognising and articulating their symptoms and have a poor perception of symptoms over time, and children of all ages may be reluctant to answer, often deferring to the opinions of their elders in a culture which promotes hierarchical respect. Changing caregivers, meant that adults were sometimes unsure of the child's symptoms over the preceding month, particularly at night or during the school

day. To date, a clinically meaningful difference in cACT has not been established; in adults the minimally important difference in ACT (a 5-item questionnaire, with a response range of 5-25 points) is 3 points.[264]

Given the lack of other studies using non-medical staff for task-shifting, we deliberately set a short follow-up period for this pilot study, to minimise loss to follow up and maximise the chances of identifying a benefit or harm from this novel approach. Overall completeness of data collection was good, including acceptable and repeatable spirometry data for over 75% of participants. We were unable to collect RCT outcome data for six (5%) participants, and post-intervention outcome data for a further 10 participants as study activities were disrupted by the global COVID19 pandemic in April-May 2020.

We relied upon self-report of symptoms, exacerbations and inhaler use: recall bias is a potential limitation of our study. We tried to quantify medication use by weighing inhalers but abandoned this approach as very few participants brought their inhaler cannisters, despite timely reminders. Our study recruited patients attending outpatient follow up at a tertiary hospital – we would expect a high rate of previous hospital admissions and attendances, since many patients are referred to this clinic from paediatric wards and the emergency department, and our findings may not represent asthmatic children more broadly in Malawi. Despite these limitations, our findings suggest that optimisation of inhaled treatment, supported by asthma education, delivered by non-clinical staff, can have a beneficial effect on asthma outcomes.

Malawi suffers from a shortage of trained medical staff with 2 physicians and 28 nurses per 100,000 population, well below the WHO “critical shortage” threshold of 2.5 health professionals (including doctors, nurses and midwives) per 1000 population.[8,9] This huge deficit in workforce requires an alternative approach to health care delivery: task shifting has been successfully employed in the community case management of childhood illnesses, and to improve access to HIV screening and treatment in Malawi.[341,376] Considering asthma management specifically, a study from rural Cameroon, reported decreased

asthma attacks over time in a group of mostly adult patients attending a nurse-led asthma clinic, although over 40% of patients were lost to follow up.[348] Task-shifting asthma education to non-medical cadres has been explored in high-income settings. Comparable outcomes were reported for asthma education delivered by lay people and nurses to adult patients, however among adolescent asthmatics the evidence for lay-led peer support interventions is weak.[320,322] The use of lay educators has not previously been evaluated in LMIC: we propose that the potential impact may be greater than in HIC, due to lower baseline education and health literacy levels among poorer populations.

These promising pilot data require further exploration of task-shifting in low-income settings, with asthma education delivered to children and adults attending a range of health care settings, and assessment of outcomes extending beyond 3-months. The reliable and affordable supply of inhaled medication, across all levels of health facilities, is also a key component to reducing the burden of asthma symptoms on patients and their families and is a major issue which must be addressed in many low-income countries.[19] Furthermore, there is a pressing need to assess the clinical and cost-effectiveness of current therapeutic approaches, using combination corticosteroid and beta-agonist inhalers, as-needed or regularly depending on symptoms, which are becoming widely used in high-income countries.[377]

5.5 List of appendices for Chapter 5

- Ethical approval from College of Medicine Research Ethics Committee (Malawi)
- Ethical approval from Liverpool School of Tropical Medicine (UK)
- Registration with Pan African Clinical Trials Registry
- Participant information sheet for children – English
- Participant information sheet for parents – English
- Assent form - English
- Consent form – English
- cACT – English
- Baseline Questionnaire – English/Chichewa
- Review Questionnaire – English/Chichewa
- Chichewa versions of study documents and SOPs available on request
    - SOP – enrolment, consent and randomisation
    - SOP – study visits
    - SOP – safety monitoring
    - SOP – FeNO measurement with NOBreath
    - SOP – COHb measurement with Rad57
    - SOP – spirometry
    - SOP – exercise challenge

6 Task-shifting to improve asthma education at a tertiary hospital in Malawi: a qualitative analysis

6.1 Introduction

This chapter describes a qualitative sub-study of the randomised-controlled trial (RCT) reported in Chapter 5, designed to provide a complementary evaluation of the task-shifting asthma education component specifically.

Asthma education is central to Global Initiative for Asthma (GINA) recommendations, which emphasise the importance of a strong partnership between patients and health care providers.[44] Achieving good symptom control is a primary goal in asthma management and adherence to treatment plays a key role.[44] Children are more likely to take their medication regularly if their family have a positive view of asthma, understand the need for regular inhalers and trust the medication.[375] During childhood, parents or carers are primarily responsible for medication administration, identification and avoidance of triggers and obtaining prescriptions.[378] However, older children can take an increasingly active role is self-management of their asthma.[379] Successful asthma care then requires that both children and parents receive adequate information on asthma, triggers, medication and self-management of symptoms.

Asthma care in LMIC is delivered in overburdened health care settings, with conflicting clinical priorities, human resource constraints and inadequate infrastructure. The general paediatric clinic at Queen Elizabeth Central Hospital (QECH), provided the “standard care” received by our RCT participants and was the sole recruitment site for the study. Children with a wide range of clinical conditions, in addition to asthma, are reviewed in this clinic, including; epilepsy, recurrent anaemia, jaundice, neurodevelopmental, renal, rheumatological, behavioural and psychological conditions. Within this busy and unstructured clinical environment, clinical staff have very limited

time to spend on each patient consultation, or to dedicate to asthma education.

Considering this, we designed an intervention, described in section 5.2.5, to improve asthma care at QECH, with individualised asthma education delivered by non-clinical staff. Task-shifting has been suggested as an effective and affordable strategy to improve the management of non-communicable diseases in LMIC, however there are limited data relating to asthma care specifically, and the use of non-clinical personnel has not been explored.[346,348]

This qualitative sub-study aimed to explore the experiences of the children, carers and study staff involved in the asthma education sessions, in order to: 1) assess the acceptability of using non-clinical staff to deliver asthma education; 2) understand facilitators and barriers to asthma education; 3) assess the perceived value of the education sessions to children and their carers.

6.2 Methods

6.2.1 Study site and context

Details of the study site, participants and RCT intervention have been reported in Chapter 5, section 5.2, including specific information regarding the asthma education intervention; pre-study training programme for the lay educators (Table 5-1), asthma education session content and checklist (Table 5-2), and Asthma Action Plan (Figure 5-1).

In total, 120 participants were recruited to the RCT between September 2018 and December 2019; 113 child-adult pairs participated in the asthma education session, either as part of the RCT intervention group or, for those in the RCT standard care group, in the 3-months following RCT completion. The qualitative assessment of the asthma education intervention was conducted between August 2019 and March 2020.

Children were most frequently accompanied to the education session by their mother (85/113, 75.2%), followed by their father (10/113, 8.8%), with the remaining adults a mix of other family members or guardians (Table 6-1).

Table 6-1. Details of adults participating in the asthma education session

	N (%)
Relationship to patient	
Mother	85 (75.2)
Father	10 (8.8)
Grandmother	8 (7.1)
Grandfather	1 (0.9)
Other female relative / guardian	3 (2.7)
Other male relative / guardian	6 (5.3)
Total female carers	96 (85.0)
Total male carers	17 (15.0)
Level of education attended	
None	3 (2.7)
Primary	37 (32.7)
Secondary	52 (46.0)
College	21 (18.6)

For one-third of accompanying adults, the highest level of education attended was primary school (37/113, 32.7%), with 52/113 (46.0%) attending secondary school and 21/113 (18.6%) attending college.

6.2.2 Study design

The sub-study used qualitative research methods including focus group discussions (FGDs) with study participants and their carers and key informant interviews with study staff (Table 6-2).[380] These aimed to gain deeper insight into the facilitators and barriers to the educational aspect of the intervention. FGDs and interviews were conducted in Chichewa, facilitated by a fluent Chichewa-speaker who had no previous involvement in the study intervention (LN); recordings were transcribed verbatim and translated into English for further analysis (LN).

Table 6-2. Details of study participants and qualitative data collection methods

Method and data source	Number of participants	Data collected
Focus Group Discussions		
Mothers and other female carers	21 (3 FGDs)	Exploring the children's and carers' experience of the asthma education including facilitators and barriers to the intervention, their perceptions of the lay educators as non-clinical staff delivering asthma education, their perceived value of the asthma education, and recommendations for future interventions
Fathers and other male carers	7 (1 FGD)	
Children	15 (2 FGDs)	
Total FGD participants	43	
Key informant interviews		
Lay educators	4, individual interviews	Lay educators' experience of delivering asthma education, their training and mechanisms for support, perceived benefits to the participants, facilitators and barriers to delivery, and recommendations
Research nurse	1, individual interview	Exploring her experience in supervising the lay educators, facilitators and barriers to the delivery and uptake of the asthma education, and recommendations
Total interview participants	5	

Participants were approached following completion of the intervention: children and their carers were purposively sampled to ensure that key participant characteristics, including age, sex, and asthma severity, and a range of views were represented. Children over the age of 10 years were invited to attend: we were concerned that younger children would be too nervous or inhibited to participate freely. Only parents or carers who attended the asthma education sessions were included. Male and female carers and children attended separate FGDs to encourage free participation.

Individual interviews were conducted with each of the "lay educators" and with the research nurse who had supervised the sessions. Interviews took

place in a private location, with full confidentiality assured to encourage honest and open participation.

6.2.3 Data analysis

Data analysis was conducted iteratively alongside data collection, to allow exploration of emerging issues in later interviews and FGDs. A thematic approach was adopted, with transcripts reviewed by three independent researchers (SR, LN and FL). A coding framework was developed (SR, LN and FL) which was used to manually code all the transcripts through identification of informative texts and quotations, with senior oversight by a post-doctoral social scientist (FL).[381] The codes were grouped into key themes derived from study objectives (deductively) and emerging from the transcripts (inductively).[382]

6.2.4 Ethical approval

Ethical approval was obtained in Malawi and the UK, as per section 5.2.10. Written informed consent was obtained from the carers and the study staff, with additional assent from the children.

6.3 Results

Four key themes emerged from the FGDs and in-depth interviews, discussed in the following sub-sections; 1. challenges with asthma care in Blantyre; 2. acceptability of using non-clinical staff as educators; 3. perceived value of asthma education; 4. facilitators and barriers to asthma education, including recommendations. We have synthesized the sub-themes, to illustrate the dimensions of an ideal task shifting asthma education intervention in Figure 6-1, at the end of the results section.

6.3.1 Challenges with asthma care in Blantyre

6.3.1.1 *Clinical environment*

Participants reported several previous challenges in accessing asthma care. Both parents and children commented that health care workers did not have enough time to explain the various aspects of asthma management, both

during admissions and outpatient attendances, largely due to the busy clinical environment. Parents felt unable to ask all the questions they had about their child's medication and asthma more generally.

> *"…the explanation there is really brief, and you will be lucky if you find a person that is able to answer any question that you have because they are very busy." Mother of 12-year-old asthmatic child, FGD.*

In addition, some parents and children also expressed their concerns about hostile attitudes they had encountered from some medical staff previously, which affected their willingness to ask for clarification when needed. Children also reported they were given conflicting information from different doctors, which was confusing.

> *"Some doctors get really angry and annoyed when you keep asking questions." Mother of 11-year-old asthmatic child, FGD.*

> *"We kept on meeting different doctors at the clinic, that was really disturbing me because you end up being told different things by different people." 13-year-old male asthmatic, FGD.*

6.3.1.2 *Access to information*

Another challenge reported by both parents and children was the lack of asthma information provided by health care staff. Some parents expressed their lack of knowledge of what the disease (asthma) is and how it affects the human body. Specific areas of concern were what to do during an asthma attack and how to administer inhaled medication. Children said they were not aware of the triggers of their asthma or the importance of using inhaled treatments.

> *"When I go to the hospital, I don't even know what exactly asthma is. But then I can't start asking the doctor because he is already busy with so many kids to be helped so I can't sit down and start asking him "Doctor please tell us what exactly asthma is*

and what should I do to help my child?"" Mother of 6-year-old asthmatic child, FGD.

"In fact, I didn't even know that asthma causes the airways to close but when we came here, they started teaching us from there" Father of 7-year-old child, FGD.

6.3.1.3 *Access to medication*

Access to inhaled medication was also expressed as a challenge, especially by parents, with inhaled medication largely unavailable at primary health centres. Parents described extremely stressful situations when they had no medication to use at home during a severe attack.

"She was attacked at around 10 in the night, we didn't have an inhaler. So, we tried making phone calls to try and find an inhaler from other people, but we didn't find it. And then we tried looking for transport, we still didn't find it. We were only able to get to the hospital at 4 in the morning." Father of 14-year-old asthmatic child, FGD.

6.3.2 Acceptability of using non-clinicians as educators

6.3.2.1 *Perspectives of patients and families*

The parents did not express any concerns that the education sessions were delivered by non-medical personnel. Some of the parents said they assumed the educators had some medical training because of their professional manner. Many parents praised the educators' overall competence and asthma-related expertise. The children said the lay educators were friendly and caring and that they felt free to ask questions without fear of being shouted at. Parents also said the openness and friendliness of the educators made the children look forward to coming back for the next study appointment.

"The kids were very happy and comfortable around them and were not afraid of them….. They were not scaring them but made them feel like they have found a friend." Mother of 9-year-old asthmatic child, FGD.

6.3.2.2 *Perspectives of the study team*

The lay educators said they were initially nervous to conduct the asthma education sessions with patients and their families. They reported that their knowledge on asthma was very limited before they participated in the training, after which they understood more about the disease and how to deliver the sessions. The educators also commented that they gained confidence to deliver the education sessions over time, with ongoing experience.

6.3.3 Perceived value of asthma education

Participants described various aspects of their lives before the asthma education intervention and the subsequent impact of the education they had received (Table 6-3).

Children who previously were frequently sick and often missed school due to their asthma described a great improvement since implementing what they had learnt during the asthma education sessions. The improvement in clinical condition had a positive impact on daily family life, with families reporting reduced school absence and increased productivity at work.

> *"When it's time for me to go to the village to farm, seeing that she won't be able to stay without being monitored, I was withdrawing her from her school here in town and I would go with her to the village. But all that stopped now - I am able to leave her." Mother of 13-year-old asthmatic child, FGD.*

Table 6-3. Participant's perceptions of the impact of asthma education on knowledge levels, symptom control and aspects of daily life.

Before asthma education intervention	After asthma education intervention
Participants' reports of asthma knowledge	
No clear understanding of asthma, common triggers and inhaled medications. Unable to identify asthma symptoms.	Improved knowledge of asthma, common triggers and inhaled medications. Greater understanding of what to do in an emergency. Confidence to identify symptoms of asthma and manage appropriately.
Participants' reports of asthma symptoms	
Difficulties breathing at night, often interfering with sleep. Frequent cough and wheeze. Frequent visits to health facilities. Frequent school absence.	Families able to manage asthma symptoms more effectively. Fewer attacks, school absence and hospital visits.
Interaction between asthma and family life	
Disruption to sleep for whole family. Stressful situations during deteriorating symptoms. Staying home to care for child. Removing child from school to allow closer monitoring.	Greater control of asthma. Knowledge of asthma triggers and self-management has reduced child's symptoms and enabled parents to be more productive. Improved asthma knowledge among wider family, including other asthmatic individuals.
Interaction between asthma and school life	
Stigmatised by peers. Lack of understanding among school community. Belief that asthma is contagious.	Children gaining support from peers through greater openness and understanding.
Interaction between asthma and the community	
Negative attitudes towards inhaled treatment. Belief in healing through traditional medicines and prayers.	Parents keen to act as asthma advocates and share their new knowledge with the wider community.

Parents were previously stressed about how to manage their child's asthma, particularly during an attack, and how to use their medication but reported increased confidence and a feeling of control, as a result of their increased knowledge levels.

"Most times…. when the child starts to get sick, we would not do anything. We would wait till maybe two days pass and then start off to the hospital. But when we were taught, it really helped…. When he gets sick again, before it reaches the point of taking him to the hospital, because of what we learnt in the research we are able to help him control the asthma before it gets worse." Mother of 7-year old asthmatic child, FGD

Both parents and children reported misconceptions and negative opinions relating to asthma and inhaled medication which they had experienced from family members, school peers and the wider community.

"When I am at school and I have asthma symptoms, my friends tell me that I am bewitched and when I am trying to play with them, they tell me that I will spread my asthma to them." 11-year-old asthmatic male, FGD.

"Some of my friends scared me saying "That is a bad drug, if your child starts using inhalers now, his asthma will never improve and will be dependent on inhalers all his life." I was really scared so much that when I got home with him, I didn't use the inhalers, I just kept them." Mother of 6-year-old asthmatic child, FGD

6.3.4 Facilitators and barriers to asthma education

6.3.4.1 *Intervention design: training, resources and support*

The lay educators and the study nurse mentioned specific resources which were helpful in ensuring the education sessions were delivered effectively.

The lay educators explained that the pre-study training they received was one of the main activities that helped them gain knowledge and confidence to deliver the sessions effectively.

"I am not a medical person but because we were specially trained, and we paid attention to the things we were being taught during the training, we were able to teach these people the same things." Asthma educator, interview

The educators also reported that that education session checklist ensured that everyone was teaching information uniformly, was helpful in reminding the educators of their own training and helped staff to focus while teaching the participants.

> *"We also need to have a paper which has the guidelines ….which helps us follow through as we are talking to them to see what has been discussed and what hasn't been mentioned yet and we tick what we have already said… it helps us not to forget because without the guidelines, it's easy to forget." Lay educator, interview*

Some parents highlighted the importance of providing additional written information, to reinforce the asthma education they had received. Written information would allow participants to revisit the information at a later date and also help share the knowledge with the wider community.

Both the educators and study nurse mentioned that the support given by supervisors and peers was also essential in ensuring the educators delivered the sessions effectively. The study nurse reported that she was available to the educators to help answer any questions and provide any additional support as needed. The educators also described the positive and motivating effect of words of appreciation from the study participants.

> *"The other form of support was from the patients, if a person compliments and appreciates the work you have done for them…, you get motivated because you feel that you have done a good job, that encourages you in the next session… so when we are working we need to encourage each other." Study nurse, interview.*

6.3.4.2 *Individual and open approach to education sessions*

Both children and their carers said the lay educators were very approachable, patient and friendly which helped in understanding the asthma education sessions. The parents also said the educators ensured they felt comfortable to ask any questions that they had about their child's condition or asthma more generally. The educators described the importance of building a good rapport

with their patients when meeting them for the first time as this ensured that everyone was open and free to learn and ask questions.

> *"First of all, we build a rapport in order to create an environment for both participant and guardian to feel that they are free…. they shouldn't be afraid of anything." Lay educator, interview.*

Lay educators said the difference in levels of education of the parents was one of the main barriers to the delivery of asthma education. Although the session was delivered in Chichewa, which parents appreciated, some still found it challenging to follow the content.

The educators explained that due to different baseline education levels among parents and children, they made sure that information was delivered according to an individual's ability to understand and paused frequently to check comprehension and give clarification. Parents appreciated the physical demonstration of inhaler administration techniques, using a bottle spacer.

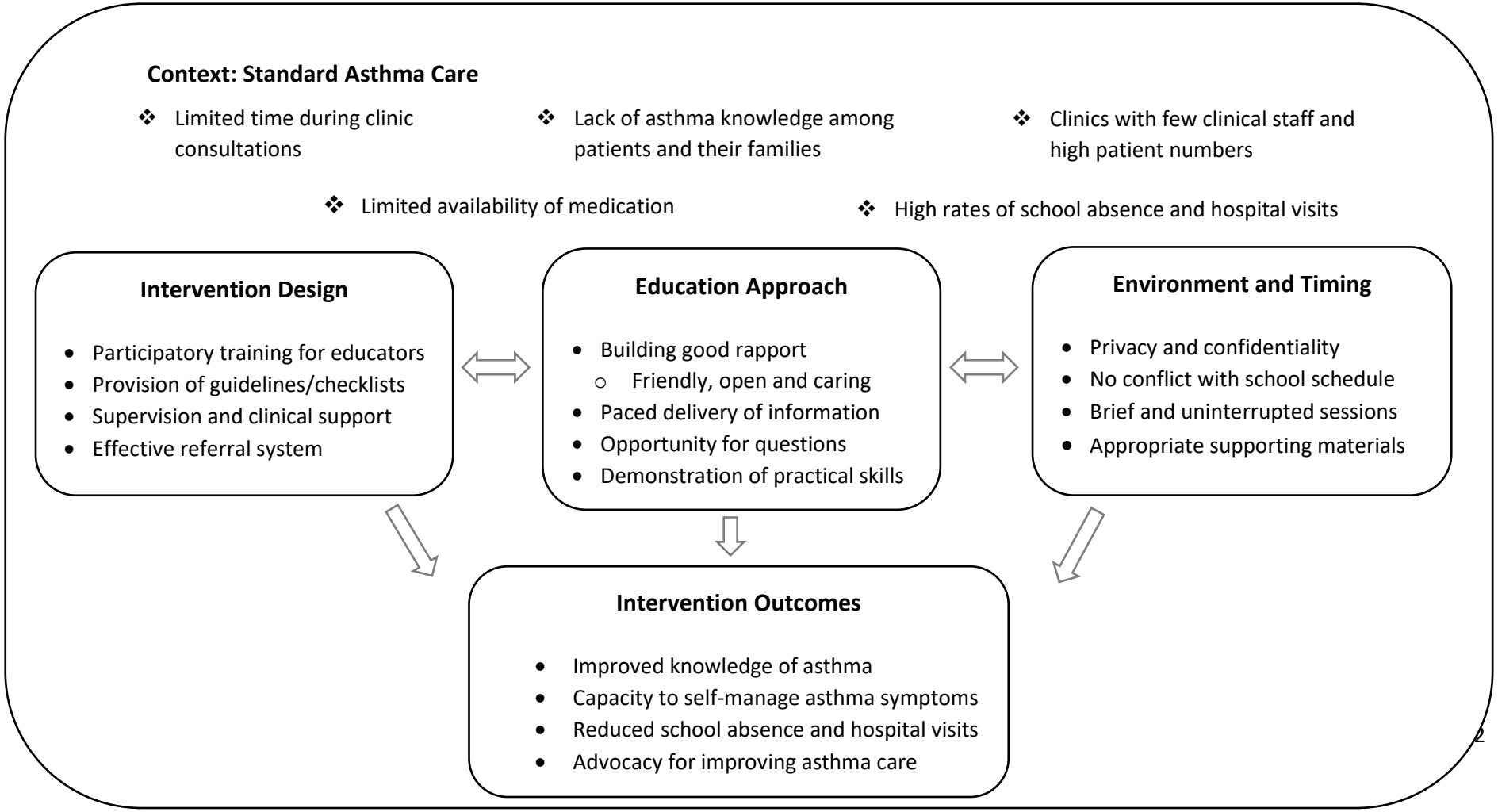
> *"…something else that that slows us down is the level of understanding of the parents. This is mostly because of the level of education that most of them have because you may explain to them clearly then ask them to explain what you just explained but you find that they are finding it hard to do that. So, we still take some time to explain again because we just have to spend that time to teach these parents so that they understand." Lay educator, interview.*

6.3.4.3 *Logistics: Location and schedule*

Both the parents and children recommended that asthma education sessions should be conducted in a private and well-sheltered location.

Some of the children reported that the education sessions interrupted their school schedule, and that this was problematic – however, others commented that this disruption was acceptable, due to the beneficial nature of the education sessions.

Figure 6-1. Task shifting of asthma education to lay educators: dimensions of an ideal intervention



6.4 Discussion

To our knowledge this is the first evaluation of an asthma education task-shifting intervention in sSA, in which asthma education is delivered by lay educators with no medical or nursing background. Patients and their parents expressed high levels of satisfaction and described the positive impact of asthma education on their knowledge levels, frequency of asthma symptoms and daily life. Families reported increased confidence to self-manage asthma attacks at home, resulting in less absence from school and work, and fewer emergency health facility attendances. The educators emphasized the importance of building a good rapport with the patient and their family, and pacing the delivery of information, considering the participants' background educational level. Young people and their families appreciated the open and friendly approach of the educators, and the time and patience that were taken to ensure understanding and address all their questions. We found that asthma education can be delivered successfully by non-clinical personnel, given adequate training and ongoing support from clinical staff, and that this approach was popular with young people and their families. However, educators and participants encountered challenges with limited space for the study activities, compromising privacy, and leaving the sessions open to interruptions and distractions.

The rationale for task-shifting, in a country with a critical shortage of health care providers has been previously discussed in section 5.4.

In Malawi, task shifting of HIV screening to non-medical cadres has been successfully deployed with lay counsellors delivering HIV counselling and testing with good programme outcomes.[341] Health Surveillance Assistants (HSAs: non-clinician health workers, with 10-weeks of basic training) have also been employed to deliver community case management of childhood illnesses; in common with our findings and others, the importance of ongoing support and supervision were highlighted in an evaluation of this scheme.[337,376] Also in common with our study, recognition by the community

and positive feedback were also mentioned as motivating factors for the HSAs.[345]

In high-income settings, a small number of studies have evaluated peer- and lay-led complex asthma interventions for adolescents, suggesting a small improvement in asthma-related quality of life, although the effect on asthma control, exacerbations and adherence are unclear.[320] Self-management education delivered to adults with asthma by trained lay people, resulted in comparable clinical outcomes to patients seen by primary care based practice nurses in the UK.[322] Qualitative exploration of the experiences of these lay educators reinforced several of the points raised in our study; the need for comprehensive support and monitoring, particularly at the start of the programme, and the importance of training, with consideration of content, intensity, and interactive teaching methods.[324]

In the USA, asthma education delivered by trained lay volunteers to families of inner-city children with asthma, during an acute hospital admission, was associated with improved asthma management behaviours.[325] Improved asthma outcomes have been associated with greater health literacy and asthma knowledge among asthmatic children's parents, consistent with our participants' responses; however, research exploring health literacy in children is scarce.[383,384] Our educators experienced particular challenges with carers who had a lower level of general education; one-third of accompanying adults had only attended school at primary level. However, compared to national levels, our participants were relatively well educated, reflecting the population of urban Blantyre. Overall in Malawi, among those aged 15-49 years, 26% of women and 36% of men have at least some secondary education, compared to 46% among our carers, with only 3% women and 5% men attending tertiary education, compared to 19% among our carers.[10]

Our qualitative sub-study sampled the experiences of a range of participants involved in the asthma education sessions, exploring the perspectives of those receiving and those providing education, and deliberately sought to include male and female carers, allowing triangulation of our findings. It is possible

that those agreeing to participate in this sub-study had a more positive view of the intervention; however, participants were purposively sampled and only three parents declined to participate, with the main reason given being time constraints. To ensure that participants felt comfortable to freely express their opinions of the study, the FGDs and interviews were facilitated by an independent researcher, with no previous connection to the RCT participants.

In conclusion, asthma education delivered by lay educators was well received by children and their families, with reported positive benefits on asthma knowledge levels, symptoms, and daily life, and increased confidence relating to asthma self-management. Further research is needed; to evaluate the wider implementation of this approach, including both clinical and cost-effectiveness, beyond a tertiary hospital setting, and to explore optimal ways to train, support and motivate lay educators in LMIC settings.

6.5 List of appendices for Chapter 6

- Ethical approvals and study documents (consent, assent, participant information sheets) as for Chapter 5

7 Summary and implications

This thesis includes four studies, designed to address some of the knowledge gaps relating to NCD-L in Malawi. The broad aims were; 1. To explore the prevalence of non-communicable lung disease and air pollution associated determinants in children and adults in rural Malawi 2. Evaluate a novel task shifting approach to asthma management for children.

This chapter summarises the rationale for the studies, the main findings and implications for policy and decision making, including recommendations for further research.

Conducting research can be challenging in low-income settings, particularly in rural areas where infrastructure is lacking, communication is difficult and health literacy levels are low. In rural Malawi, the setting for the Chikhwawa studies (Chapters 3 and 4), most adults have only spent approximately 3-years at school (median length of schooling; 2.7 years for women, 3.4 years for men).[10] Less than half of all rural households own a mobile phone, and only 3.9% of households have electricity to charge it.[10]

Research activities can arouse considerable suspicion among local communities, especially in rural areas. Field work was disrupted during late 2017 due to unrest among many communities in southern Malawi, relating to concerns of vampirism. This impacted negatively on the final phases of data collection for both Chikhwawa studies. We also observed that many participants, especially older people, were reluctant to perform spirometry. Participants voiced fears relating to the spirometry equipment and there was a concern that older individuals were “too weak” to participate, despite having no objective contraindications.

Poor rural communities rely heavily on subsistence farming and are highly vulnerable to climatic shocks. During the 3-year follow-up of the adult Chikhwawa cohort, the region experienced severe flooding, crop failures and famine. Many homes were destroyed, including personal possessions and

study documentation, and families relocated. Tracing of participants was particularly challenging, hence the relatively high rates of loss to follow-up. The field team also experienced challenges in explaining to community members the differences between Malawi-Liverpool-Wellcome Trust, as a research organisation, and the various aid agencies that were operating in the area as part of disaster relief activities.

Despite these considerable challenges, we collected and published the first data from sSA relating to lung function and personal air pollution exposure in children, and longitudinal lung function and personal air pollution exposure in adults, as summarised in section 7.1.

For health systems and policy makers to address the growing global burden of NCDs, it is essential to understand the size and nature of the problem. Due to shortcomings in information systems and routine record keeping, it is often difficult to gain such insight. Within routine clinical care, it has previously proved impossible to accurately quantify the number of asthmatic children attending the general Paediatric outpatient clinic at Queen Elizabeth Central Hospital (QECH), or to assess the extent of their symptoms or responses to treatment. Shortages in staffing and a large and unpredictable workload mean that routine care adopts a “firefighting” approach; the target is to review all patients who have attended, suffering a wide variety of medical conditions, and ensure they have received appropriate medications within the clinic and hospital pharmacy opening hours. Structured clinical assessment and subsequent adjustment of asthma treatment, and patient education are frequently suboptimal. The randomised-controlled trial and qualitative sub-study described in Chapters 5 and 6 aimed to provide baseline information on the clinical characteristics of asthmatic children in Blantyre, and to assess the feasibility, acceptability and effectiveness of a task-shifting intervention on asthma outcomes. This is the first comprehensive description of a paediatric asthmatic cohort from a low-income sSA country, and the first trial of task shifting asthma education to non-clinical staff in a resource-limited setting, as summarised in section 7.2

7.1 Prevalence and determinants of NCD-L in children and adults in rural Malawi

The cross-sectional and cohort studies presented in Chapters 3 and 4 respectively, aimed to assess the prevalence and determinants of chronic respiratory symptoms, spirometric abnormalities and personal exposure to air pollution in children and adults living in Chikhwawa, Malawi. Furthermore, we aimed to explore the lung function trajectories of adults, over a period of 3-years, to assess whether biomass smoke exposure causes an accelerated decline in lung function, in the same way as tobacco smoke exposure.

Adults and children were recruited from the same rural communities that had participated in the Cooking And Pneumonia Study (CAPS), which facilitated secondary analyses to explore the effect of the cookstove intervention. During the CAPS trial (2013-2016), intervention households received two cleaner-burning biomass-fuelled cookstoves, while control households continued cooking using traditional methods, mostly open fires.[26] We compared lung function between children in the CAPS intervention and control households and explored adult lung function trajectories, with "access to a cookstove" included as a covariate in the mixed-effects lung function model.

Children reported a high burden of chronic respiratory symptoms, mainly cough (8.0%) and wheeze (7.1%), with half of wheezing children experiencing severe symptoms, according to ISAAC definitions. In keeping with previous reports from Malawi, we found high rates of chronic respiratory symptoms (13.6% at baseline), particularly cough (11.1%) among the adult cohort.[22,23]

Using GLI African-American reference equations, we found similar lung function z-scores for children and adults; mean (SD) FEV_1 -0.48 (0.93) and -0.38 (1.14), and mean (SD) FVC -0.30 (0.96) and -0.19 (1.09), for children and adults respectively.[57] This suggests that lung function deficits in adulthood are likely to have origins in early childhood, before the age of 6 years. The prevalence of decreased FVC in the adult population is highly dependent on the comparative reference range used: the prevalence is much lower when

Malawian lung function data are compared to African-American reference ranges (either NHANES III or GLI) supporting ancestral differences in lung physiology, the prognostic significance of which is unknown.

Both children and adults were exposed to high peak levels of personal air pollution exposure. In children, maximum CO exposure and COHb levels exceeded WHO guidelines in 50.1% and 68.5% of participants, respectively, however median CO exposure was 0.20 ppm (IQR, 0.07-0.54).[350] In adults, median CO exposure was 1.27 ppm (IQR, 0.79-2.05) and median personal $PM_{2.5}$ 77.0 $\mu g/m^3$ (IQR, 42.8-153.1), almost three times the WHO air quality 24-hour exposure limit.[350]

Overall, we found no evidence of an association between respiratory symptoms, spirometric indices and measures of personal air pollution exposure (CO and COHb in children, CO and $PM_{2.5}$ in adults). It is possible that exposure to biomass smoke, largely from intermittent cooking activities, does not deliver a sufficiently sustained or concentrated dose of harmful pollutants to lead to adverse respiratory effects.

Exploring the longitudinal lung function data, we found no evidence of accelerated lung function decline among this cohort of biomass smoke exposed adults. Annual rates of FEV_1 and FVC decline were 30.9ml (95% CI: 21.6-40.1) and 38.3ml (95% CI: 28.5-48.1) respectively, comparable to healthy non-smokers in HIC.[222] Previous TB and BMI were significantly associated with lung function. Although exposure to $PM_{2.5}$ was decreased in those with access to a cookstove, we found no evidence that having access to a cookstove affected adult lung function.

In children, however, results signalled a benefit from the cookstove intervention: children from the CAPS intervention households had lower median COHb levels (3.50% vs 4.85%, p=0.006) and higher FVC z-scores (-0.22 vs -0.44, p=0.05) than controls. These results of exploratory secondary analyses are interesting, given the apparent lack of association between personal air pollution exposure and lung function, and require cautious

interpretation. However, it is plausible that the cookstove intervention had a positive effect during a critical period of lung growth and development in younger children: the CLHS participants were aged 3-6 years during the CAPS trial period.

Neither CLHS or ALHS were designed to assess the impact of the cookstove intervention on personal air pollution exposure or lung function: the primary outcome reported in CAPS was WHO Integrated Management of Childhood Illness defined pneumonia in children aged under 5 years.[26] Since CAPS, CLHS and ALHS recruited participants from the same village communities in Chikhwawa, we have taken the opportunity to explore secondary research questions relating to the cookstove intervention, permitted by overlapping study participation.

Several factors may have influenced the impact of the cookstove intervention on air pollution exposure and respiratory outcomes. Most households in Chikhwawa cook outdoors; only households with an eligible child (aged ≤4½ years) were recruited from the village clusters and so their local environment may have been contaminated by emissions from neighbouring households not included in the CAPS trial. Furthermore, other sources of ambient air pollution, such as burning rubbish and clay brick ovens are common in Chikhwawa. Cookstove malfunction was relatively common during the trial period, and cookstove use waned among intervention households, with most households using a combination of cooking methods (both cookstove and traditional open-fire).[26]

In summary, the novel findings in Chapters 3 and 4 suggest that, in a rural Malawian community;

- Lung function deficits in adulthood are more likely due to early life factors (acting before age 6 years) than accelerated age-related decline
- Biomass smoke (measured by $PM_{2.5}$ and CO personal exposure levels) does not appear to affect lung function or respiratory symptoms

- A cleaner-burning cookstove intervention did not influence lung function in adults although there was a signal of benefit in younger children which warrants further investigation

Future public health interventions to promote lung health must address factors acting in early life (*in utero* and early childhood) and consider multi-faceted clean air interventions.

7.2 Evaluation of a task shifting approach to asthma management for children in Malawi

7.2.1 Clinical characteristics of asthmatic children in urban Blantyre

To my knowledge, there is no previously published data relating to asthmatic children in Malawi. The first aim of the study presented in Chapter 5 was to describe the clinical characteristics of children attending outpatient follow-up at a tertiary hospital in urban Blantyre. We recruited 120 children, aged 6-15 years with a previous "doctor-diagnosis" of asthma from the general paediatric clinic at QECH, Blantyre and assessed asthma symptoms, recent exacerbations, asthma treatment, and potential risk factors. We found a high baseline level of asthma symptoms and exacerbations. In the previous 3-months; one-quarter of children had been admitted to hospital, a further third had attended a health facility for emergency care, although not requiring admission, and two-thirds had missed school, due to asthma symptoms. By GINA criteria, 85% of participants had uncontrolled or partly controlled symptoms. Despite the high burden of symptoms, less than half had been prescribed regular ICS and the mean daily beclometasone dose was relatively low.

We measured pre-intervention FeNO levels in 113 children; levels were high (median FeNO 41.5 ppb [IQR 25.0-63.0]) suggesting that eosinophilic asthma is the predominant phenotype in Malawian children, and that treatment with ICS is appropriate. Spirometric abnormalities were common with one-third of

patients demonstrating airway obstruction pre-intervention (FEV_1/FVC ratio below LLN) and weak correlation between symptom score and FEV_1/FVC.

7.2.2 Can an enhanced asthma care package improve asthma outcomes?

Chapter 5 reports an RCT, which aimed to assess the feasibility and effectiveness of an enhanced asthma care package, including 1) a standardised assessment of asthma control, 2) optimisation of treatment according to standard guidelines and 3) an education intervention for children and their carers, delivered by non-clinical staff. 120 children were stratified according to their baseline level of asthma control and randomised to either continue with standard care in the general paediatric clinic at QECH, or to receive an enhanced care package, with clinical outcomes compared at 3-months.

We found a significant difference between groups in the primary outcome, asthma control (measured by cACT score); a mean (SD) increase in cACT score of 2.7 (2.8) points for intervention patients compared to 0.6 (2.8) points for those receiving standard care. Fewer children in the enhanced care group experienced asthma exacerbations requiring hospital admission, emergency health facility attendance, and school absence. Children in the enhanced care group were prescribed a significantly higher daily dose of beclometasone at 3-months, although there was no difference in FeNO levels between the two groups. Children with lower pre-intervention cACT score or FEV_1/FVC ratio showed a greater response to the intervention.

7.2.3 Experiences of asthma education delivered by non-medical personnel

The qualitative sub-study of the RCT, aimed to assess to acceptability and perceived value of the asthma education intervention, and explore facilitators and barriers to this approach. Young people, carers and study staff expressed high levels of satisfaction relating to the education sessions. Participants described the positive impact of asthma education on their knowledge levels; increased confidence to self-manage symptoms resulted in less absence from school and work, and fewer emergency health care attendances. Good rapport, with open dialogue between the educators, children and carers, was

essential and an individualised approach allowed educators to tailor the education session to the participants' background level of knowledge and understanding. Educators highlighted the importance of adequate training, written resources and ongoing supportive supervision.

In summary, the novel findings of chapters 5 and 6 suggest that among asthmatic children attending a hospital outpatient clinic in Blantyre, Malawi;

- The burden of asthma symptoms is high, with frequent school absence
- Eosinophilic airway inflammation is common, and therefore treatment with ICS is highly appropriate
- Task shifting of asthma education to lay educators is a feasible, acceptable and effective approach to improve asthma outcomes

Further research is needed to see if our task shifting approach to asthma education could be more widely employed, across all levels of health care facility. Alternative approaches to empower asthmatic patients and their families, and educate the wider community are also needed.

7.3 Towards solutions

There remain large gaps in our knowledge relating to NCD-L across the life course in Malawi, and sSA more widely, with key questions regarding effective disease prevention strategies and health care delivery.

Potential multi-sectoral public health interventions to tackle early life risk factors and optimise lung growth and development (Figure 7-1) could include;

- Strategies to improve engagement with antenatal and postnatal care at health facility level; group antenatal care, involvement of fathers, health promotion (breastfeeding, improved hygiene practices, seeking early medical care) by non-medical staff
- Targeted antenatal nutritional interventions e.g. vitamin D
- Multifaceted clean air interventions

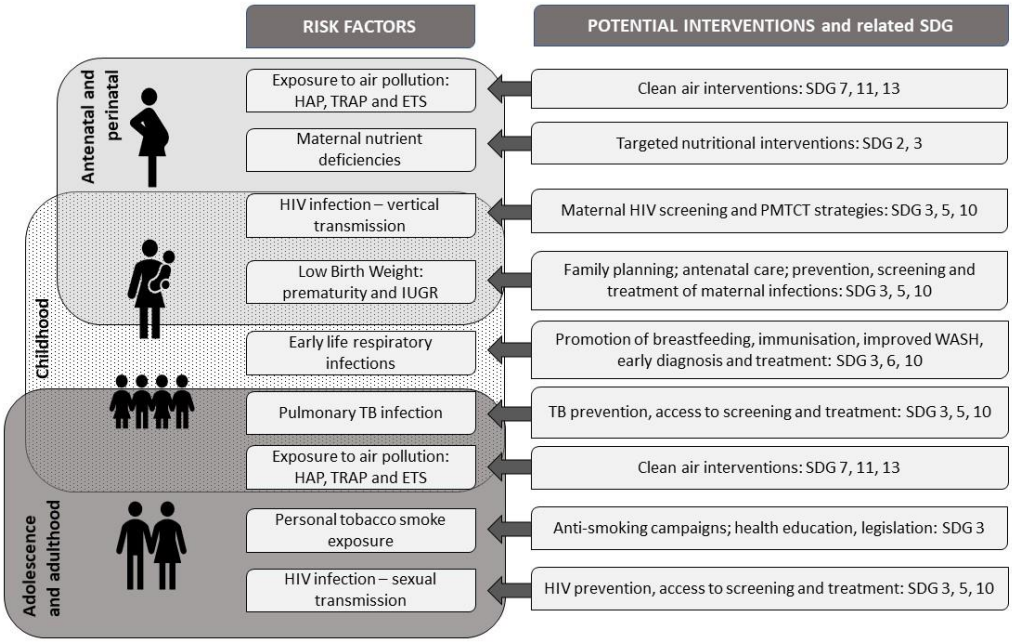


Figure 7-1 Risk factors for poor lung health in sSA and potential interventions.

ETS, environmental tobacco smoke; HAP, household air pollution; IUGR, intrauterine growth restriction; PMTCT, prevention of mother-to-child transmission; SDG, sustainable development goal; TB, tuberculosis; TRAP, traffic-related air pollution; WASH, water, sanitation and hygiene

There are many unanswered questions relating to the management of NCDs in the poorest parts of the world including;

- How best to engage communities and empower patients and their families?
- How to improve access to effective clinical care, including appropriate diagnosis, treatment and monitoring of chronic conditions?
- Can task shifting and the use of lay educators be deployed more widely, across a range of medical conditions and community settings?

Future research to inform health care practice and policy in LIC must address local priorities and include all relevant stakeholders. In this way, patients, health care providers, policy makers and researchers can explore strategies to deliver effective clinical care of chronic conditions, such as asthma, with direct relevance to resource-limited settings.

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9 Appendices

UNIVERSITY OF MALAWI

CERTIFICATE OF ETHICS APPROVAL

This is to certify that the College of Medicine Research and Ethics Committee (COMREC) has reviewed and approved a study entitled:

P.07/16/1994 – Child lung health and exposure to household air pollution in rural Malawi (Abbreviated title: Child lung health study) version 4.0 dated 10/10/16 by Dr. S. Rylance

On 31st October 2016

As you proceed with the implementation of your study, we would like you to adhere to international ethical guidelines, national guidelines and all requirements by COMREC as indicated on the next page

Dr. C. Dzamalala- Chairperson (COMREC)

Approved by
College of Medicine
31 OCT 2016
(COMREC)
Research and Ethics Committee

31st October 2016
Date

REQUIREMENTS FOR ALL COMREC APPROVED RESEARCH PROTOCOLS

1. Pay the research overhead fees as required by the College of Medicine for all approved studies.

2. You should note that the COMREC Sub-Committee on Research Participants' Safety will monitor the conduct of the approved protocol and any deviation from the approved protocol may result in your study being stopped.

3. You will provide an interim report in the course of the study and an end of study report.

4. You are required to obtain a continuation approval after 12 months from the date of approval.

5. All investigators who are Medical Practitioners must be fully registered with the Medical Council of Malawi.

Dr Sarah Rylance
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Friday, 02 December 2016

Dear Dr Rylance,

Research Protocol **(16-040) Child lung health and exposure to household air pollution in rural Malawi**

Thank you for your letter of 1st December 2016 providing the necessary in-country approvals for this project. I can confirm that the protocol now has formal ethical approval from the LSTM Research Ethics Committee.

The approval is for a fixed period of three years and will therefore expire on 1st December 2019. The committee may suspend or withdraw ethical approval at any time if appropriate.

Approval is conditional upon:

- Continued adherence to all in-country ethical requirements.
- Notification of all amendments to the protocol for approval before implementation.
- Notification of when the project actually starts.
- Provision of an annual update to the Committee.
  Failure to do so could result in suspension of the study without further notice.
- Reporting of new information relevant to patient safety to the Committee
- Provision of Data Monitoring Committee reports (if applicable) to the Committee

Failure to comply with these requirements is a breach of the LSTM Research Code of Conduct and will result in withdrawal of approval and may lead to disciplinary action. The Committee would also like to receive copies of the final report once the study is completed. Please quote your Ethics Reference number with all correspondence.

Yours sincerely

Dr Angela Obasi
Chair
LSTM Research Ethics Committee

Child Lung Health Study – Study information sheet (English version v5, 01/02/17)

University of Malawi College of Medicine
Malawi Liverpool Wellcome Trust
Liverpool School of Tropical Medicine

Child Lung Health Study – a cross sectional survey of children aged 6-8 years living in Chikhwawa, Malawi.

1. **Introduction.**

We would like to learn more about lung problems which affect young children in Malawi. There is very little research in Africa looking at problems such as ongoing cough, wheeze and breathlessness in this age group.

We will study how much of a problem ongoing cough, wheeze and breathlessness is in children and what the causes might be. This work will help us develop solutions to the problems we find.

2. **Why has your child been chosen?**

Your household is in one of the villages that took part in a trial called the Cooking And Pneumonia Study (CAPS). CAPS investigated whether using a new type of cookstove might improve the health of young children and adults. The Child Lung Health Study will include children living in households in villages that took part in CAPS. Your household has been chosen because your household is in one of the villages that took part in CAPS and your child has been chosen because he or she is in the age range (6 to 8 years) making him or her suitable.

3. **Does your child have to take part in the study?**

We will only ask you to participate in this study if your village leaders have agreed for your village to participate. You do not have to take part even if other members of the village agree to take part. Your agreement to help with this research study is completely optional and if you would prefer not to participate, this will be without penalty or loss of benefits to which you would be otherwise entitled. You can choose to leave the study at any time, without providing a reason.

4. **What will be involved if you agree for your child to take part in this study?**

We will make an appointment to visit you and your child at home.

We will ask you some questions about your child's health and record the results on a small computer. These will include questions about symptoms such as cough and wheeze, previous TB or chest infections and your child's HIV status.

We will measure your child's weight using scales, height using a ruler and upper arm circumference.

We will ask your child to blow into a machine which measures how their lungs are working. The study staff will then give them 4 puffs of a Salbutamol inhaler to try and improve the way their lungs work. We will then ask your child to blow into the machine again. It can take a little while to get a good result and we will ask your child to repeat the blowing test at least 3 times, up to a maximum of 8 attempts.

We will place a small peg-like device on your child's finger for a few moments to take a measurement of the levels of carbon monoxide in their body. This measurement does not involve taking a blood sample and does not hurt.

We will place a small air pollution monitor on your child's clothing for 2 day to allow us to measure air pollution exposure. This will not interfere with their usual daily activities.

We do not need to take any blood samples for this study.

5. Will there be any risks involved in the study?

You and your child may be inconvenienced by the time commitment involved in taking part in the study, the information we need to record and the measurements we need to take. All of the study procedures are routine and involve minimal risks. Your child may feel a bit light headed when they blow hard into the machine, but they will be sitting securely in a chair for the test and the nurses are trained to look out for this. The medicine (called Salbutamol) that your child will be given to improve their lung function is regularly taken by children with asthma. The dose is very low and therefore side effects such as racing heart and jitteriness are very unlikely.

6. Will there be any benefits involved in being in the study?

Our overall aim is to improve the care of children with ongoing respiratory symptoms. If we find your child has a lung problem we can refer them to a health centre for further investigation and treatment.

To thank your child for taking part, we will give them a school bag. We will also provide the household with items such as sugar and salt, as compensation for the time and effort involved during the 2-day period of air pollution monitoring.

7. Who is organizing the study?

The research is being done by researchers at the College of Medicine, Malawi Liverpool Wellcome Trust, Liverpool School of Tropical Medicine, and Queen Mary University of London.

8. Who will know what we find out?

We will record the information we collect about you using a small computer. This information will be transferred to a computer database but without using your name or address so that you could not be identified from this information. This database will be analyzed by researchers at the College of Medicine, Malawi Liverpool Wellcome Trust and Liverpool School of Tropical Medicine. We will share the results of this study with you and your community, at local charity or research meetings and will present the findings at an international conference and in journals. We will not share any information that would allow you to be identified

9. What happens if I change my mind?

If you agree to join the study you can change your mind and withdraw your consent at any time. If you have any questions about this study, please contact our Senior Field Co-ordinator, Andrew Naunje on [+265 999981414].

For any questions regarding participant rights in the scope of this study, please contact the chairman of the local ethics committee (COMREC). This committee has reviewed and approved all of these studies. The contact details are: COMREC Secretariat, College of Medicine, P/bag 360, Blantyre 3. Tel no: [01871911 ext 334].

Child Lung Health Study
Consent form for parent/guardian of child
English version v5, 01/02/17

Name of parent/guardian:

Name of child:

Participant ID number:

Address:

1	Have you read or listened to the participant information sheet (v5, 01/02/17)?	YES	NO
2	Have you had the opportunity to ask questions?	YES	NO
3	Have your questions been answered, and do you feel that you have had enough information about this study?	YES	NO
4	Do you understand that you are free to withdraw from the study at any time without giving a reason and without any penalties?	YES	NO
5	Do you understand that data collected during the study may be looked at by individuals from Liverpool School of Tropical Medicine and regulatory authorities? All information will be anonymised.	YES	NO

If you have answered 'yes' to questions 1-5 please sign the form, or place a thumbprint below, which means that you voluntarily agree to enter the study.

I voluntarily agree to enter this study.

Signature/Thumbprint		Date
Witness to consent if participant unable to sign their name		
Name in capitals		
Signature		Date
Please tick to confirm that the child has been asked and is happy to take part in the study ☐		
Investigator obtaining consent		
Name in capitals		
Signature		Date

Child Lung Health Study
Participant questionnaire
English version v5, 01/02/17

To be administered by CLHS staff using Kobotoolbox form

Section 1	General data
Section 2	BOLD cough
Section 3	BOLD phlegm
Section 4	BOLD breathlessness
Section 5	ISAAC core asthma 6/7 years
Section 6	ISAAC core rhinitis 6/7 years
Section 7	ISAAC core eczema 6/7 years
Section 8	Respiratory questions

Section 1

1.1 How old is your child?

1 digit number

1.2 What is your child's date of birth?

--/--/---- (Date/Month/Year)

1.3 Are they male or female?

Male (code=1) / Female (code=2)

1.4 Does your child attend school?

Yes (code=1) / No (code=0)

1.5 On average, how many hours do they spend away from home each day?

1 digit number

1.6 Does your child help with the cooking?

Yes (code=1) / No (code=0) / Don't know (code=9)

1.7 If yes, how times each day?

1 digit number

Section 2

2.1 Does your child usually cough when they don't have a cold?

Yes (code=1) / No (code=0) / Don't know (code=9)

2.2 Are there months in which they cough on most days?

Yes (code=1) / No (code=0) / Don't know (code=9)

2.3 Do they cough on most days for as much as three months each year?

Yes (code=1) / No (code=0) / Don't know (code=9)

2.4 For how many years have they had this cough?

1 digit number

Section 3

3.1 Does your child usually bring up phlegm from their chest when they don't have a cold?

Yes (code=1) / No (code=0) / Don't know (code=9)

3.2 Are there months in which they have this phlegm on most days?

Yes (code=1) / No (code=0) / Don't know (code=9)

3.3 Do they bring up phlegm on most days for as much as three months each year?

Yes (code=1) / No (code=0) / Don't know (code=9)

3.4 For how many years have they had this phlegm?

1 digit number

Section 4

4.1 Is your child unable to walk due to a condition other than shortness of breath?

Yes (code=1) / No (code=0) / Don't know (code=9)

4.2 Is your child troubled by shortness of breath when hurrying on the level or walking up a slight hill?

Yes (code=1) / No (code=0) / Don't know (code=9)

4.3 Does your child have to walk slower than children of their age on level ground because of shortness of breath?

Yes (code=1) / No (code=0) / Don't know (code=9)

4.4 Does your child ever have to stop for breath when walking at their own pace on level ground?

Yes (code=1) / No (code=0) / Don't know (code=9)

4.5 Is your child too short of breath to leave the house or short of breath on dressing or undressing?

Yes (code=1) / No (code=0) / Don't know (code=9)

4.6 Have breathing problems interfered with your child's usual daily activities or caused them to miss school?

Yes (code=1) / No (code=0) / Don't know (code=9)

If yes, how many times has this happened in the past 12 months?

Section 5

5.1 Have your child ever had wheezing or whistling in the chest at any time in the past?

Yes (code=1) / No (code=0) / Don't know (code=9)

If no, please skip to question 5.6

5.2 Has your child had wheezing or whistling in the chest in the past 12 months?

Yes (code=1) / No (code=0) / Don't know (code=9)

If no, please skip to question 5.6

5.3 How many attacks of wheezing has your child had in the past 12 months?

None (code=0)/ 1 to 3 (code=1)/ 4 to 12 (code=2) / More than 12 (code=3)

5.4 In the past 12 months how often, on average, has your child's sleep been disturbed due to wheezing?

Never (code=0)/ Less than one night per week (code=1)/ One or more nights per week (code=2)

5.5 In the past 12 months has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths?

Yes (code=1) / No (code=0) / Don't know (code=9)

5.6 Has your child ever had asthma?

Yes (code=1) / No (code=0) / Don't know (code=9)

5.7 In the past 12 months has your child's chest sounded wheezy during or after exercise?

Yes (code=1) / No (code=0) / Don't know (code=9)

5.8 In the past 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?

Yes (code=1) / No (code=0) / Don't know (code=9)

Section 6

6.1 Has your child ever had a problem with sneezing, or a runny or blocked nose when they DID NOT have a cold or the flu?

Yes (code=1) / No (code=0) / Don't know (code=9)

If no, please skip to question 6.6

6.2 In the past 12 months, has your child had a problem with sneezing, or a runny or blocked nose when they DID NOT have a cold or the flu?

Yes (code=1) / No (code=0) / Don't know (code=9)

If no, please skip to question 6.6

6.3 In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?

Yes (code=1) / No (code=0) / Don't know (code=9)

6.4 In which of the past 12 months did this nose problem occur? (Tick any which apply)

January / February / March / April / May / June / July / August / September / October / November / December (code = 1/2/3/4/5/6/7/8/9/10/11/12)

6.5 In the past 12 months, how much did this nose problem interfere with your child's daily activities?

Not at all (code=0) / A little (code=1) / A moderate amount (code=2) / A lot (code=3)

6.6 Has your child ever had hayfever?

Yes (code=1) / No (code=0) / Don't know (code=9)

Section 7

7.1 Has your child ever had an itchy rash which was coming and going for at least six months?

Yes (code=1) / No (code=0) / Don't know (code=9)

If no, please skip to question 7.7

7.2 Has your child had this itchy rash at any time in the past 12 months?

Yes (code=1) / No (code=0) / Don't know (code=9)

If no, please skip to question 7.7

7.3 Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?

Yes (code=1) / No (code=0) / Don't know (code=9)

7.4 At what age did this itchy rash first occur?

Under 2 years (code=1) / 2 to 4 years (code=2) / Age 5 years or more (code=3)

7.5 Has this rash cleared completely at any time during the past 12 months?

Yes (code=1) / No (code=0) / Don't know (code=9)

7.6 In the past 12 months, how often, on average, has your child been kept awake at night by this itchy rash?

Never (code=0)/ Less than one night per week (code=1)/ One or more nights per week (code=2)

7.7 Has your child ever had eczema?

Yes (code=1) / No (code=0) / Don't know (code=9)

Section 8

8.1 Has your child ever been admitted to hospital with severe cough or difficulty breathing?

Yes (code=1) / No (code=0) / Don't know (code=9)

If no, skip to question 8.5

8.2 How many times has this happened?

One or two digit number

8.3 How old were they when this happened the first time?

One digit (age in years, if less than 1 year enter 0)

8.4 How old were they when this happened the last time?

One digit (age in years, if less than 1 year enter 0)

8.5 Has your child been treated with antibiotics for a chest problem in the last year?

Yes (code=1) / No (code=0) / Don't know (code=9)

8.6 If yes, how many times?

One or two digit number

8.7 Has your child ever been treated for TB?

Yes (code=1) / No (code=0) / Don't know (code=9)

8.8 Has anyone living in the house been treated for TB, since this child (the participant) was born?

Yes (code=1) / No (code=0) / Don't know (code=9)

8.9 Has your child ever had an HIV test?

Yes (code=1) / No (code=0) / Don't know (code=9)

8.10 If yes, what was the result?

HIV negative (code=0)/ HIV positive (code=1)/ Don't know (code=9)

8.11 Is your child taking any regular medicines?

ART / Cotrimoxazole / other (please list)

Questions relating to cooking methods, parental smoking, poverty markers will be obtained from adult household member as part of Adult Lung Health Study.

CERTIFICATE OF ETHICS APPROVAL

This is to certify that the College of Medicine Research and Ethics Committee (COMREC) has reviewed and approved a study entitled:

P.04/18/2384 - A randomised controlled trial of an enhanced asthma care package vs standard outpatient care on asthma control in Malawian children version 2.3 dated 21 May 2018 by Dr Sarah Rylance

Approved by College of Medicine Research and Ethics Committee (COMREC) 23 JUN 2018

On 23-Jun-18

As you proceed with the implementation of your study, we would like you to adhere to international ethical guidelines, national guidelines and all requirements by COMREC as indicated on the next page

Dr. YB. Mlombe – Chairperson (COMREC)

23-Jun-18

Date

REQUIREMENTS FOR ALL COMREC APPROVED RESEARCH PROTOCOLS

1. Pay the research overhead fees as required by the College of Medicine for all approved studies.

2. You should note that the COMREC Sub-Committee on Research Participants' Safety will monitor the conduct of the approved protocol and any deviation from the approved protocol may result in your study being stopped.

3. You will provide an interim report in the course of the study and an end of study report.

4. All COMREC approvals of new applications and progress reports are valid for one year only. Therefore all approved studies running for more than one year are subject to continuing review annually. You are required to submit a progress report to COMREC within 90-30 days before the expiration date. Your current expiration date is 23-Jun-19. Studies shall be considered lapsed and inactive if continuing review application is not received one month after the expiry of the previous approval. In that case, all study related operations should cease immediately except those that are necessary for the welfare of subjects.

5. All investigators who are Medical Practitioners must be fully registered with the Medical Council of Malawi.

Dr Sarah Rylance
Malawi-Liverpool-Wellcome Trust Clinical Research Programme
PO Box 30096
Chichiri
Blantyre 3
Malawi

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Thursday, 12 July 2018

Dear Dr Rylance,

Research Protocol (18-018) 'A randomised controlled trial of enhanced asthma care package vs standard outpatient care on asthma control in Malawian children'

Thank you for your correspondence of 2 July 2018 providing the necessary in-country approvals for this project. I can confirm that the protocol now has formal ethical approval from the LSTM Research Ethics Committee.

The approval is for a fixed period of three years and will therefore expire on 11 July 2018. The Committee may suspend or withdraw ethical approval at any time if appropriate.

Approval is conditional upon:

- Continued adherence to all in-country ethical requirements.
- Notification of all amendments to the protocol for approval before implementation.
- Notification of when the project actually starts.
- Provision of an annual update to the Committee.
  Failure to do so could result in suspension of the study without further notice.
- Reporting of new information relevant to patient safety to the Committee
- Provision of Data Monitoring Committee reports (if applicable) to the Committee

Failure to comply with these requirements is a breach of the LSTM Research Code of Conduct and will result in withdrawal of approval and may lead to disciplinary action. The Committee would also like to receive copies of the final report once the study is completed. Please quote your Ethics Reference number with all correspondence.

Yours sincerely

Dr Angela Obasi
Chair
LSTM Research Ethics Committee

09 July 2018

To Whom It May Concern:

RE: A randomised controlled trial of an enhanced asthma care package vs standard outpatient care on asthma control in Malawian children.

As project manager for the Pan African Clinical Trial Registry (www.pactr.org) database, it is my pleasure to inform you that your application to our registry has been accepted. Your unique identification number for the registry is **PACTR201807211617031**.

Please be advised that you are responsible for updating your trial, or for informing us of changes to your trial.

Additionally, please provide us with copies of your ethical clearance letters as we must have these on file (via email or post or by uploading online) at your earliest convenience if you have not already done so.

Please do not hesitate to contact us at +27 21 938 0835 or email epienaar@mrc.ac.za should you have any questions.

Yours faithfully,

Elizabeth D Pienaar
www.pactr.orgProject Manager
+27 021 938 0835

Childhood asthma study

1. What is research?

Research is a way we try to find out the answers to questions.

2. Why is the project being done?

The research is being done to learn more about asthma in Malawian children. We want to see how well the treatments that you take for your asthma are working.

3. What is asthma?

Having asthma means that the little tubes that take air into your lungs sometimes don't work very well. That can make if difficult for you to breathe, and you might you cough or wheeze.

4. Why me?

You have been chosen because you are being treated for asthma at the children's clinic in Queen Elizabeth Central Hospital

5. Do I have to take part?

No, it is your decision whether to join the study and you can always change your mind. If you do not join the study, you can still come to the clinic and see the doctors for your asthma.

6. What will happen?

If you agree to take part we will choose whether you start in group A or group B.

Group A: We will ask you and your guardian some questions about your asthma. We will see you again for some more questions after 3-months. Then if you choose, you can move to group B.

Group B: You will come for an extra visit to the clinic. During this visit we will do some tests to check your lungs and ask you questions about your asthma.

We will measure how tall you are and how much you weigh.

We will ask you to blow into a machine to test the air that comes out of your lungs.

We will ask you to blow into another machine called a spirometer. Then we will give you 4 puffs of your inhaler and repeat the test.

We may ask you to repeat the blowing tests several times, to get a good result.

We will ask you to run around for 6 minutes and then ask you to blow into the spirometer again.

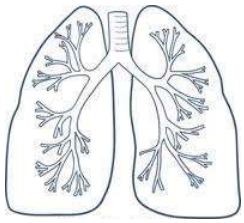
We will put a clip on your finger to measure the level of oxygen in your body.

None of the tests will hurt at all. If you want to stop the tests or have a rest, you can just tell us.

Then we will ask you to breath in some steamy salty water and cough up, into a small pot.

Now you can have a rest and we will give you something to eat and drink.

We will talk to you about asthma and the treatments that you should take.



We will see you again after 6 weeks, if we think your asthma treatment needs improving.

We will see everyone after 3-months to ask some more questions about your asthma.

You may be invited by the study team to take part in a small group meeting. We would like to know how you found the education session and understand how we can improve it. The discussion will be recorded so that we can listen to it again later. The information will be kept private and it is your decision to take part.

7. What if something goes wrong?

Your doctor thinks that is is safe for you to do these tests. We will be looking after you carefully during the study visit. If you feel unwell at all, we will stop the tests and give you your asthma medicine (inhaler).

8. Will taking part help me?

During the study we will spend time teaching you about asthma and trying to improve your treatment.

9. What happens when the research study stops?

The research will be talked about and written down, but no-one will know that you took part. All your information will be kept private.

10. What if I don't want to do the research anymore?

Just tell your parents and the study team that you do not want to take part any more. You don't have to give a reason. It is your choice.

11. Did anyone else check the study is OK to do?

Before any research can start, it is checked by a group of experts, to make sure that the research is fair.

12. How can I find out more about this study?

If you have any questions, please ask Dr. Sarah Rylance or any of the the study team.

Phenotyping Asthmatic Children – Study information sheet (English)

University of Malawi College of Medicine
Malawi Liverpool Wellcome Trust
Liverpool School of Tropical Medicine

1. **Introduction.**

We would like to learn more about asthma in Malawian children, to try and improve the treatment your child receives. In asthma, the small airways in the lungs become swollen and narrow causing cough, wheeze and difficulty in breathing. Children with asthma may share similar features (phenotypes) and they may respond to treatment differently. Knowing more about these shared features may help us to understand the causes of asthma and to give the best treatment.

2. **Why has my child been chosen?**

We are collecting information from all children attending the asthma clinic at Queen Elizabeth Central Hospital (QECH), to see how much of a problem their asthma is.

Children will be chosen at random to attend for an extra visit, during which we will make a detailed assessment of their asthma, provide some asthma education and make changes to their treatment if needed.

3. **Does my child have to take part in the study?**

It is your choice whether or not your child takes part. If you or your child would prefer not to, your child will continue to be reviewed in the asthma clinic and receive all treatment, as before. You or your child can choose to leave the study at any time, without providing a reason.

4. **What will be involved if you agree for your child to take part in this study?**

Half of the children will be chosen at random for a detailed asthma assessment, asthma education and adjustment of their asthma treatment if needed (group B). Half the children will continue to receive care in the general clinic (group A).

If your child is in group A, we will ask you some questions before you leave clinic today, and contact you again in 3-months to attend for a study visit. If the study supervisors are happy that the assessment and treatment in group B have been well tolerated /safe, we will offer you the opportunity to attend for the detailed assessment and education session, after the trial finishes.

If your child is in group B, we will make an appointment for your child to come for an extra appointment at the hospital.

During the assessment….

We will ask you some questions about your child's health and record the results on a small computer. These will include questions about your child's asthma, problems relating to their health, and the treatment they receive.

We will measure your child's weight using scales, height using a ruler and upper arm circumference.

We will perform several tests to look at how inflamed your child's airways are – this helps to see if your child's current treatment is working.

a. **FeNO**

We will ask your child to breathe slowly into a cardboard tube attached to a small machine. This will take about 10 seconds. We may repeat the test up to 3 times, with a 5-minute rest in between attempts.

b. Spirometry

We will ask your child to blow into a machine which measures how their lungs are working. The study staff will then give them 4 puffs of a Salbutamol inhaler to try and improve the way their lungs work. We will then ask your child to blow into the machine again. It can take a little while to get a good result and we will ask your child to repeat the blowing test at least 3 times, up to a maximum of 8 attempts.

c. Sputum induction

We will ask your child to breath a steam (made from salt water) in and out for 5 minutes, then we will ask them to cough up into a small pot. We will repeat this up to 4 times, until your child has coughed up enough sputum.

d. Exercise challenge

We will ask your child to run outside, as fast as they can, for 6 minutes. At the end, we will check their heart rate and oxygen levels with a small plastic clip attached to their finger. Then they will rest and we will check their lung function (spirometry) after 5, 10 and 15 minutes.

e. Chest X-ray

If the doctor thinks it will be helpful, your child will be sent for a chest x-ray in the X-ray Department at QECH.

f. Carboxyhaemoglobin measurement

We will place a small plastic clip on your child's finger for a few moments to take a measurement of the levels of carbon monoxide in their body. This measurement does not involve taking a blood sample and does not hurt.

Following the assessment, we will spend some time talking to you and your child about asthma and their treatment. The doctor will adjust the treatment to try and improve your child's asthma. We will arrange to review your child again, after 3 months and repeat some of the tests. If your child's asthma needs closer monitoring, we will arrange to see them after 6 weeks.

After completion of 3-months in group B

a. Focus group discussions and interviews

You and your child may be invited by the study team to participate in a small group discussion or one-to-one interview. We are interested to know how you have found the education session and to understand how we can improve the experience. The sessions will be recorded so that we can listen again later to the conversation. The information will be kept confidentially and it is you and your child's decision whether you would like to take part in the discussions.

After the 3-month study period, we will continue to follow-up all children in the general clinic, and will repeat any assessments needed as part of clinical care.

5. Will there be any risks involved in the study?

Some of the tests are designed to test how sensitive your child's airways are. There is therefore a small chance that performing the test may bring on asthma symptoms. These tests are part of

normal asthma care in Europe and the USA and are not considered dangerous in any way. We will check your child's lung function before and during the tests, so that we can quickly detect any problem. If your child does become wheezy, the test will be stopped immediately and we will give treatment to stop the symptoms. A senior nurse or doctor will always be present when the tests are being performed.

6. Will there be any benefits involved in being in the study?

During the study visit, your child will have a thorough assessment by a senior children's doctor. At the moment these tests are only available to study patients, as they are not part of routine asthma care in Malawi. All results will be explained to you and your child during asthma clinic follow-up visits, as soon as they are available. It is possible that participation in the study will lead to an improvement in your child's asthma treatment. Overall, we hope that the study will lead to better asthma care for children in Malawi.

The assessment will take several hours and may be tiring for your child. You will receive compensation for your time, travel and inconvenience for attending study visits (outside of normal clinic appointments), in keeping with current COMREC guidance (~10USD)

7. Who is organizing the study?

The study is led by Dr. Sarah Rylance, the Senior doctor in charge of the asthma clinic at QECH. Dr. Rylance is working with Malawi Liverpool Wellcome Trust and Liverpool School of Tropical Medicine.

Other researchers supervising the study are from; Liverpool School of Tropical Medicine, Queen Mary University of London, and Lancaster University in the UK.

8. Who will know what we find out?

We will record the information we collect about your child using a computer. This information will be transferred to a computer database with the child's name removed, so that they cannot be identified from this information. The information will be stored securely for 5-years. Dr. Rylance will have responsibility for the asthma clinic file, which will contain your child's medical record – this will be stored in a secure location within QECH.

The results of the study will be shared at research meetings (in Malawi and overseas) and will be published in medical journals, so that other doctors and patients can benefit from our findings.

9. What happens if I change my mind?

If you agree to join the study you can change your mind and withdraw your consent at any time. If you have any questions about this study, please contact our Senior Research Nurse, Beatrice Chinoko on [+265 0998319218].

The local ethics committee (COMREC) has reviewed and approved this study – any problems that cannot be addressed by the study team, should be directed to:

COMREC Secretariat, College of Medicine, P/bag 360, Blantyre 3. Tel no: [01871911 ext. 334].

Phenotyping Asthmatic Children (PAC)
Assent form for children
English version v1.1, 02/04/2019

Participant ID number:

Please circle yes / no

1	Have you read or listened to the participant information sheet for children (v1.1, 02/04/2019)?	YES	NO
2	Do you understand what the study is about?	YES	NO
3	Do you understand that you may be invited to take part in a group discussion about the education session?	YES	NO
4	Have you asked all the questions you want?	YES	NO
5	Have your questions been answered in a way you understand?	YES	NO
6	Do you understand that you can stop being in the study at any time, without giving a reason?	YES	NO
7	Are you happy to take part?	YES	NO

If any answers are "No" or you don't want to take part, do no write your name!

If you ***do*** want to take part, you can write your name below.

Name/Thumbprint		Date
Witness to consent if child unable to write their name		
Name in capitals		
Signature		Date
Investigator obtaining consent		
Name in capitals		
Signature		Date

Phenotyping Asthmatic Children (PAC)
Consent form
English version v2.4, 02/04/2019

Participant ID number:

Please circle yes / no

1	Have you read or listened to the participant information sheet (v2.4, 02/04/2019)?	YES	NO
2	Have you had the opportunity to ask questions?	YES	NO
3	Have your questions been answered, and do you feel that you have had enough information about this study?	YES	NO
4	Do you understand that you are free to withdraw from the study at any time without giving a reason and without any penalties?	YES	NO
5	Do you understand that you may be invited by the study team to be involved in a small group discussion or one-to-one interview after going through the intervention?	YES	NO
6	Do you understand that data collected during the study may be looked at by individuals from Liverpool School of Tropical Medicine and regulatory authorities? All information will be anonymised.	YES	NO

If you have answered 'yes' to questions 1-5 please sign the form, or place a thumbprint below, which means that you voluntarily agree to enter the study.

I voluntarily agree to enter this study. YES / NO

Name of child		
Name of parent/guardian		
Signature/Thumbprint		Date
Witness to consent if participant unable to sign their name		
Name in capitals		
Signature		Date
Please tick to confirm that the child has been asked and is happy to take part in the study ☐		
Investigator obtaining consent		
Name in capitals		
Signature		Date

Have your child complete these questions.

1. How is your asthma today?

SCORE

 0 Very bad	 1 Bad	 2 Good	 3 Very good	☐

2. How much of a problem is your asthma when you run, exercise or play sports?

 0 It's a big problem, I can't do what I want to do.	 1 It's a problem and I don't like it.	 2 It's a little problem but it's okay.	 3 It's not a problem.	☐

3. Do you cough because of your asthma?

 0 Yes, all of the time.	 1 Yes, most of the time.	 2 Yes, some of the time.	 3 No, none of the time.	☐

4. Do you wake up during the night because of your asthma?

 0 Yes, all of the time.	 1 Yes, most of the time.	 2 Yes, some of the time.	 3 No, none of the time.	☐

Please complete the following questions on your own

5. During the last 4 weeks, how many days did your child have any daytime asthma symptoms?

5 Not at all	4 1-3 days	3 4-10 days	2 11-18 days	1 19-24 days	0 Everyday	☐

6. During the last 4 weeks, how many days did your child wheeze during the day because of asthma?

5 Not at all	4 1-3 days	3 4-10 days	2 11-18 days	1 19-24 days	0 Everyday	☐

7. During the last 4 weeks, how many days did your child wake up during the night because of asthma?

5 Not at all	4 1-3 days	3 4-10 days	2 11-18 days	1 19-24 days	0 Everyday	☐

TOTAL ☐

Introduction

I am going to ask you some questions about your child's breathing problem / asthma. Children with asthma usually suffer with cough, wheeze and difficulty breathing, which comes and goes – these are called "symptoms". We would like to know how much of a problem their symptoms have been recently and what treatments they are taking.

Ndikufunsani mafunso okhuza mavuto amapumidwe amwana wanu / mphumu. Ana odwala mphumu nthawi zambiri amakhosomola, kuliza makwiyo, ndi kubanika, zomwe zimabwera ndi kupita – izi zimatchedwa "zizindikilo". Tikufuna tidziwe zambiri zamavuto ndi zizindikilo zake m'mene zilili pano ndi thandizo la mankhwala limene akulandira.

To be administered by study staff using KoboToolbox

Assessment of exacerbations Kuunikira m'mene nthenda yafikira poyipa		
1a	Has your child ever been admitted to hospital because of their asthma? *For example; for cough, wheeze, or difficulty breathing*	Yes / No *If no, go to Q2a*
	Kodi mwana wanu anayambapo wagonekedwa kuchipatala chifukwa cha nthenda ya mphumu? *Mwachitsanzo; kukhosomola, kuliza makwiyo, kapena kubanika.*	Eya / Ayi *Ngati ayi, pitani ku funso 2a*
1b	If yes, how many times?	Once / twice / ≥3 times
	Ngati ndi Eya, kangati?	Kamodzi / kawiri / kupyora katatu
1c	Has your child been admitted to hospital because of their asthma, in the past 3-months?	Yes / No *If no, go to Q1e*
	Kodi mwana wanu anayamba wagonekedwa kuchipatala chifukwa cha nthenda ya mphumu pamiyezi itatu yapitayi?	Eya / Ayi *Ngati ayi, pitani ku funso 1e*
1d	If yes, how many times, in the past 3-months?	*Number*
	Ngati ndi Eya anagonekedwa kangati pa miyezi itatu yapitayi?	*Number*
1e	If yes (*to 1c*), when was the last time this happened?	*Month*
	Ngati ndi Eya *(kufunso 1c),* ndiliti komaliza izi zinachitika?	*Miyezi*
1f	For each admission, how many nights did they stay in hospital?	Admission 1: Admission 2: Admission 3:
	Maulendo onse omwe anagonekedwa anagonamo usiku ungati?	Ulendo 1: Ulendo 2: Ulendo 3:
1g	*Verified with health passport (past 3-months)?*	*Yes / No / Not available*
2a	Have you ever taken your child to a health centre because of their asthma, in the past 3-months?	Yes / No *If no, go to Q3a*
	Munayambapo mwamutengera mwana wanu kuchipatala chaching'ono chifukwa cha nthenda ya mphumu pa miyezi itatu yapitayi?	Eya / Ayi, *Ngati ayi, pitani ku funso 3a*
2b	If yes, how many times?	*Number*

	Ngati ndi Eya, kangati?	*Number*
2c	If yes, when was the last time this happened?	*Month*
	Ngati ndi Eya, ndiliti komaliza izi zinachitika?	*Miyezi*
2d	*Verified with health passport?*	*Yes / No / Not available*
3a	In the past 3-months, has your child missed any days of school, because of their asthma?	Yes / No
	Pa miyezi itatu yapitayi, kodi mwana wanu anajombapo kusukulu chifukwa cha nthenda ya mphumu?	Eya / Ayi
3b	If yes, how many?	*Number*
	Ngati ndi Eya, kangati?	*Number*
Assessment of treatment Kuunukira za thandizo la mankhwala		
4	Does your child have any inhalers?	Yes / No *If no, go to Q6*
	Kodi mwana wanu ali ndi mankhwala opumira/ofayira (inhalers)	Eya / Ayi
S100 B50 B100 B200	***Please ask to see and write name and dose (show pictures)*** Choices: Salbutamol 100, Beclomethasone 50/100/200, other (please list)	
	We would like to know how they use it	-
	Tikufuna tidziwe m'mene amagwiritsira ntchito	-
a	How many puffs each time?	*Number*
	Panthawi imene akugwiritsa ntchito amafayira kangati?	*Number*
b	How many times in a day?	*Number*
	Patsiku amapanga kangati?	*Number*
c	Regularly or when needed	Regularly / when needed
	Nthawi zonse kapena akafunikira?	Nthawi zonse / akafunikira
d	With / without spacer	With spacer / without
	Ndi chipangizo cha botolo kapena ayi?	Ndichipangizo cha botolo/ ayi
	If they have a Salbutamol inhaler:	
5	What happens when they use it?	They get better / They get worse / There is no change
	Chimachitika ndi chani mukagwiritsa ntchito?	Amapeza bwino Zimaonjezereka / Sizisintha
	If they have a Beclomethasone inhaler, which they use regularly:	
6	How many times/week do you think they forget a dose?	Once / 2-4 times/ 5 or more times
	Ndi nthawi yochuluka bwanji kapena sabata imene inu mukuganizira kuti amatha kuyiwala kutenga mankhwala?	Kamodzi/ kawiri kapena kanayi / kasanu kapena kupitilira apo

7	Are they taking any other treatment for their asthma, at the moment? (tablets, syrup)	Please list
	Akumwa mankhwala a mphumu pakali pano? (mapilisi, amadzi)	Chonde fotokozani
Assessment of asthma control (GINA) Kuunikira njira zochepetsera nthenda ya mphumu		
	In the last 4 weeks, has your child had;	
	M'masabata anayi apitawo, mwana wanu wakhalapo ndi;	
8a	Daytime asthma symptoms (cough, wheeze, difficulty breathing) more than twice/week	Yes / No
	Zizindikilo za mphumu monga (kukhosomola, kuliza makwiyo, kubanika) nthawi ya masana koposera kawiri pa sabata	Eya / Ayi
8b	Any night waking due to asthma symptoms	Yes / No
	Kodi amadzuka usiku chifukwa cha zizindikilo za mphumu	Eya / Ayi
8c	Inhaler needed for symptoms more than twice/week?	Yes / No
	Kodi amafuna mankhwala opumira/ofayira amphumu kawiri pa sabata chifukwa cha zizindikilo?	Eya / Ayi
8d	Any activity limitation due to asthma (missed school, stopped sports, difficult walking/running due to symptoms)	Yes / No
	Pali zomwe amalephera kupanga chifukwa cha mphumu (kujomba ku sukulu, kuleka masewero, kuvutika kuyenda/kuthamanga chifukwa cha zizindikilo)	Eya / Ayi
ISAAC		
9a	Has your child had wheezing or whistling in the chest in the past 12 months?	Yes / No *If no, go to 8c*
	Kodi mwana wanu amamveka makwiyo m'chifuwa m'miyezi khumi ndi iwiri yapitayi?	Eya / Ayi *Ngati ayi, pitani ku funso 9c*
9b	How many attacks of wheezing has your child had in the past 12 months?	None / 1-3 / 4-12 / More than 12
	Wadwalapo makwiyo kangati m'miyezi khumi ndi iwiri yapitayi?	Palibe / 1-3 / 4-12 / Kopitilira 12
9c	In the past 12 months how often, on average, has your child's sleep been disturbed due to wheezing?	Never/ <1 night per week / ≥1 nights per week
	Miyezi 12 yapitayi zachitika pafupi pafupi bwanji kuti mwana wanu kuvutika kugona chifukwa cha makwiyo?	Sizinachitike / kosapitilira usiku umodzi pa sabata / usiku umodzi kapena kuposera apo pa sabata
9d	In the past 12 months has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths?	Yes / No
	Miyezi 12 yomwe yapitayi kulira makwiyo kwapangisa mwana wanu kuvutika kutululutsa liwu kapena mau ali mkatikati mopuma?	Eya / Ayi
9e	Has your child ever had a problem with sneezing, or a runny or blocked nose when they DID NOT have a cold or the flu?	Yes / No
	Kodi mwana wanu anakhalapo ndi vuto la ku fwenthela, kutuluka mamina kapena kutsekeka m'mphuno mwake ngakhale munthawiyo samadwala chimfine?	Eya / Ayi

9f	Has this nose problem been accompanied by itchy-watery eyes?	Yes / No
	Vuto la m'mphuno limeneli limaphatikizana ndi kutuluka kwa misozi yoyabwa m'maso?	Eya / Ayi
9g	Has your child ever had an itchy rash which was coming and going for at least six months?	Yes / No
	Kodi mwana wanu anatulukapo nsungu zoyabwa zomwe zimabwera ndi kupita kosachepera miyezi isanu ndi umodzi?	Eya / Ayi
9h	Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?	Yes / No
	Nsungu zoyabwa zinayamba zamutuluka mwana wanu m'malo monga awa: popinda nkono, kumbuyo kwa bondo, pamwamba pa kakolo, m'musi mwa matako, m'khosi, m'makutu kapena m'maso?	Eya / Ayi
Potential contributing factors Zithu zimene zimapangitsa kuonjezera nthendayi		
10	How many brothers and sisters do they have?	*Number*
	Kodi ali ndi azilongo kapena azichemwali angati?	*Number*
11	How many people live in the family home?	*Number*
	Kodi m'banja mwanu mulipo anthu angati?	*Number*
12a	Does anyone else in the family have asthma?	Yes / No / Don't know
	Alipo wina aliyense ali ndi nthenda ya mphumu m'banja mwanu?	Eya / Ayi / Sindikuziwa
12b	If yes, who in the family has asthma?	Mother/ father/ sibling/ other
	Ngati ndi Eya, ndi ndani m'banja mwanu ali ndi nthenda ya mphumu?	Amayi / abambo / chemwali kapena mlongo / ena
13	Does your child have any allergies, eg. to food, medicine?	Yes / No / Don't know
	Kodi mwana wanu ali ndi ziwengo, chitsanzo: kuzakudya kapena kumankhwala?	Eya / Ayi / Sindikuziwa
14	Does anyone smoke at home?	No-one / mother / father / other
	Alipo amene amasuta fodya pakhomo panu?	Palibe/ amayi / abambo/ ena
15	Are there any animals living inside the house?	None /Dog / Cat / Chickens / Goat / Other
	Pali ziweto zina zimene zimakhala m'nyumba mwanu?	Palibe /Galu /Mphaka /Nkhuku /Mbuzi / Zina
16	Does the family keep any animals outside the house?	None /Dog / Cat / Chickens / Guinea fowl /Goat /Sheep/ Pig / Cow / Rabbits / Horse / Donkey / other
	Kodi banja lanu limaweta ziweto izi kunja kwa nyumba?	Palibe / Galu / Mphaka / Nkhuku / Nkhanga / Mbuzi / Nkhosa / Nkhumba / Ng'ombe / Mbira / Hatchi / Bulu / zina

17	What method do the family use to cook at home?	Charcoal / Wood / Electricitiy / Gas / Coal / Crop residue / other
	Kodi banja lanu limagwiritsa ntchito moto wanji pophika pakhomo panu?	Makala / Nkhuni / Magetsi / Gasi / Malasha / Zosalira za mbeu mmunda / zina
18	What method do the family use for lighting at home?	Electricity / Gas / Kerosene / Candles / Torch / Other
	Kodi mumagwiritsa ntchito chani pofuna kuwaritsa mnyumba mwanu?	Magetsi / Gasi / Parafini / Makandulo / Matochi / zina
19	Did your child get admitted to hospital with a chest infection before the age of 1 years?	Yes / No / Don't know
	Kodi mwana wanu anayambapo wagonekedwa m'chipatala chifukwa cha vuto la pachifuwa asanakwanitse chaka chimodzi?	Eya / Ayi / Sindikuziwa
20	Were they born on time/early?	On time / Early
	Kodi amabadwa munthawi yake kapena nthawi isanakwane	Munthawi yake / nthawi yosakwanira
21	How much did they weigh when they were born?	Weight / Don't know
	Kodi amalemera bwanji atangobadwa kumene?	Kulemera / Sindikudziwa
22	At what age did your child first have any asthma symptoms?	Years
	Kodi mwana wanu anayamba koyamba liti kuonetsa zizindikilo za mphumu ali ndi zaka zingati?	Zaka
Triggers / activity levels Zoyambitsa / mulingo wa tchito zochitika		
23	Have you noticed anything that makes their asthma symptoms worse?	Dust / wind / smoke / vehicle fumes / changes in the weather / exercise / animals?
	Kodi munazindikira chimene chimapangitsa kuti zizindikilo za mphumu zikwere?	Fumbi / mphepo / utsi / utsi wa galimoto / kusintha kwa nyengo / popanga masewera / zinyama
24a	Does your child go to school?	Yes / No *If no, go to Q24*
	Mwana wanu amapita ku sukulu?	Eya / Ayi *Ngati ayi, pitani ku funso 25*
24b	If yes, which class?	Standard 1-7, form 1-4
	Ngati ndi Eya, ali mu kalasi yanji?	Standard 1-7, form 1-4
25a	What interests does the child have, at school and at home?	Running / playing games / football / singing / dancing / other
	Kodi mwana wanu amakonda chani, ku sukulu komanso pakhomo?	Kuthamanga / kusewera magemu / mpira / kuyimba / kuvina / zina
25b	How does their activity compare with their friends or siblings?	More active / less active / same
	Kodi mwana wanu ndi wochangamuka bwanji kusiyanisa ndi anzake kapena azibale ake?	Ndiwochangamuka kwambiri /

		ndiwochangamuka pang'ono / chimodzimodzi
Other medical conditions Matenda ena		
26	Does your child cough up sputum regularly?	Yes / No
	Kodi mwana wanu amakhosomola makhololo nthawi zonse?	Eya / Ayi
27	Has your child ever had whooping cough?	Yes / No / Don't know
	Kodi mwana wanu anayambapo wakhala ndi chifuwa chokoka mtima?	Eya / Ayi / Sindikuziwa
28	Has your child ever been treated for TB?	Yes / No / Don't know
	Kodi mwana wanu anayambapo walandira thandizo la matenda a chifuwa chachikulu?	Eya / Ayi / Sindikuziwa
29a	Has your child ever had an HIV test?	Yes / No / Don't know *If no / don't know, advise to attend under 5s for test*
	Kodi mwana wanu munamuyezesapo magazi kuti muziwe ngati ali ndi kachilombo ka HIV?	Eya / Ayi / Sindikuziwa *Ngati ayi kapena simukudziwa, mupite ku chipatala cha ana akamuyeze*
29b	If yes, what was the result?	HIV negative / HIV positive
	Zosatira zake zinali zotani?	Alibe ka chilombo ka HIV / Ali ndi kachilombo ka HIV

Also, please complete Childhood Asthma Control Test (paper version)

Introduction

I am going to ask you some questions about your child's breathing problem / asthma. Children with asthma usually suffer with cough, wheeze and difficulty breathing, which comes and goes – these are called "symptoms". We would like to know how much of a problem their symptoms have been recently and what treatments they are taking.

Ndikufunsani mafunso okhuza mavuto amapumidwe amwana wanu / mphumu. Ana odwala mphumu nthawi zambiri amakhosomola, kuliza makwiyo, ndi kubanika, zomwe zimabwera ndi kupita – izi zimatchedwa "zizindikilo". Tikufuna tidziwe zambiri zamavuto ndi zizindikilo zake m'mene zilili pano ndi thandizo la mankhwala limene akulandira.

To be administered by study staff using KoboToolbox

Assessment of exacerbations Kuunikira m'mene nthenda yafikira poyipa		
1a	Has your child ever been admitted to hospital because of their asthma? *For example; for cough, wheeze, or difficulty breathing*	Yes / No *If no, go to Q2a*
	Kodi mwana wanu anayambapo wagonekedwa kuchipatala chifukwa cha nthenda ya mphumu? *Mwachitsanzo; kukhosomola, kuliza makwiyo, kapena kubanika.*	Eya / Ayi *Ngati ayi, pitani ku funso 2a*
1b	If yes, how many times?	Once / twice / ≥3 times
	Ngati ndi Eya, kangati?	Kamodzi / kawiri / kupyora katatu
1c	Has your child been admitted to hospital because of their asthma, in the past 3-months?	Yes / No *If no, go to Q1e*
	Kodi mwana wanu anayamba wagonekedwa kuchipatala chifukwa cha nthenda ya mphumu pamiyezi itatu yapitayi?	Eya / Ayi *Ngati ayi, pitani ku funso 1e*
1d	If yes, how many times, in the past 3-months?	*Number*
	Ngati ndi Eya anagonekedwa kangati pa miyezi itatu yapitayi?	*Number*
1e	If yes (*to 1c*), when was the last time this happened?	*Month*
	Ngati ndi Eya *(kufunso 1c),* ndiliti komaliza izi zinachitika?	*Miyezi*
1f	For each admission, how many nights did they stay in hospital?	Admission 1: Admission 2: Admission 3:
	Maulendo onse omwe anagonekedwa anagonamo usiku ungati?	Ulendo 1: Ulendo 2: Ulendo 3:
1g	*Verified with health passport (past 3-months)?*	*Yes / No / Not available*
2a	Have you ever taken your child to a health centre because of their asthma, in the past 3-months?	Yes / No *If no, go to Q3a*
	Munayambapo mwamutengera mwana wanu kuchipatala chaching'ono chifukwa cha nthenda ya mphumu pa miyezi itatu yapitayi?	Eya / Ayi, *Ngati ayi, pitani ku funso 3a*
2b	If yes, how many times?	*Number*

	Ngati ndi Eya, kangati?	*Number*
2c	If yes, when was the last time this happened?	*Month*
	Ngati ndi Eya, ndiliti komaliza izi zinachitika?	*Miyezi*
2d	*Verified with health passport?*	*Yes / No / Not available*
3a	In the past 3-months, has your child missed any days of school, because of their asthma?	Yes / No
	Pa miyezi itatu yapitayi, kodi mwana wanu anajombapo kusukulu chifukwa cha nthenda ya mphumu?	Eya / Ayi
3b	If yes, how many?	*Number*
	Ngati ndi Eya, kangati?	*Number*
Assessment of treatment Kuunukira za thandizo la mankhwala		
4	Does your child have any inhalers?	Yes / No *If no, go to Q6*
	Kodi mwana wanu ali ndi mankhwala opumira/ofayira (inhalers)	Eya / Ayi
S100 B50 B100 B200	***Please ask to see and write name and dose (show pictures)*** Choices: Salbutamol 100, Beclomethasone 50/100/200, other (please list)	
	We would like to know how they use it	-
	Tikufuna tidziwe m'mene amagwiritsira ntchito	-
a	How many puffs each time?	*Number*
	Panthawi imene akugwiritsa ntchito amafayira kangati?	*Number*
b	How many times in a day?	*Number*
	Patsiku amapanga kangati?	*Number*
c	Regularly or when needed	Regularly / when needed
	Nthawi zonse kapena akafunikira?	Nthawi zonse / akafunikira
d	With / without spacer	With spacer / without
	Ndi chipangizo cha botolo kapena ayi?	Ndichipangizo cha botolo/ ayi
	If they have a Salbutamol inhaler:	
5	What happens when they use it?	They get better / They get worse / There is no change
	Chimachitika ndi chani mukagwiritsa ntchito?	Amapeza bwino Zimaonjezereka / Sizisintha
	If they have a Beclomethasone inhaler, which they use regularly:	
6	How many times/week do you think they forget a dose?	Once / 2-4 times/ 5 or more times
	Ndi nthawi yochuluka bwanji kapena sabata imene inu mukuganizira kuti amatha kuyiwala kutenga mankhwala?	Kamodzi/ kawiri kapena kanayi / kasanu kapena kupitilira apo

7	Are they taking any other treatment for their asthma, at the moment? (tablets, syrup)	Please list
	Akumwa mankhwala a mphumu pakali pano? (mapilisi, amadzi)	Chonde fotokozani
Assessment of asthma control (GINA) Kuunikira njira zochepetsera nthenda ya mphumu		
	In the last 4 weeks, has your child had;	
	M'masabata anayi apitawo, mwana wanu wakhalapo ndi;	
8a	Daytime asthma symptoms (cough, wheeze, difficulty breathing) more than twice/week	Yes / No
	Zizindikilo za mphumu monga (kukhosomola, kuliza makwiyo, kubanika) nthawi ya masana koposera kawiri pa sabata	Eya / Ayi
8b	Any night waking due to asthma symptoms	Yes / No
	Kodi amadzuka usiku chifukwa cha zizindikilo za mphumu	Eya / Ayi
8c	Inhaler needed for symptoms more than twice/week?	Yes / No
	Kodi amafuna mankhwala opumira/ofayira amphumu kawiri pa sabata chifukwa cha zizindikilo?	Eya / Ayi
8d	Any activity limitation due to asthma (missed school, stopped sports, difficult walking/running due to symptoms)	Yes / No
	Pali zomwe amalephera kupanga chifukwa cha mphumu (kujomba ku sukulu, kuleka masewero, kuvutika kuyenda/kuthamanga chifukwa cha zizindikilo)	Eya / Ayi

Also, please complete Childhood Asthma Control Test (paper version)

OPEN ACCESS

ORIGINAL ARTICLE

Lung health and exposure to air pollution in Malawian children (CAPS): a cross-sectional study

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ABSTRACT

Background Non-communicable lung disease and exposure to air pollution are major problems in sub-Saharan Africa. A high burden of chronic respiratory symptoms, spirometric abnormalities and air pollution exposures has been found in Malawian adults; whether the same would be true in children is unknown.

Methods This cross-sectional study of children aged 6–8 years, in rural Malawi, included households from communities participating in the Cooking and Pneumonia Study (CAPS), a trial of cleaner-burning biomass-fuelled cookstoves. We assessed; chronic respiratory symptoms, anthropometry, spirometric abnormalities (using Global Lung Initiative equations) and personal carbon monoxide (CO) exposure. Prevalence estimates were calculated, and multivariable analyses were done.

Results We recruited 804 children (mean age 7.1 years, 51.9% female), including 476 (260 intervention; 216 control) from CAPS households. Chronic respiratory symptoms (mainly cough (8.0%) and wheeze (7.1%)) were reported by 16.6% of children. Average height-for-age and weight-for-age z-scores were −1.04 and −1.10, respectively. Spirometric abnormalities (7.1% low forced vital capacity (FVC); 6.3% obstruction) were seen in 13.0% of children. Maximum CO exposure and carboxyhaemoglobin levels (COHb) exceeded WHO guidelines in 50.1% and 68.5% of children, respectively. Children from CAPS intervention households had lower COHb (median 3.50% vs 4.85%, p=0.006) and higher FVC z-scores (−0.22 vs −0.44, p=0.05) than controls.

Conclusion The substantial burden of chronic respiratory symptoms, abnormal spirometry and air pollution exposures in children in rural Malawi is concerning; effective prevention and control strategies are needed. Our finding of potential benefit in CAPS intervention households calls for further research into clean-air interventions to maximise healthy lung development in children.

Key messages

What is the key question?

► Is the high burden of chronic respiratory morbidity and household air pollution exposure described in Malawian adults, also seen in children, and would a cleaner-burning biomass-fuelled cookstove intervention have a positive effect on lung function in early life?

What is the bottom line?

► We found a substantial burden of chronic respiratory symptoms, spirometric abnormalities and carbon monoxide exposures among young children living in rural Malawi, together with a signal of beneficial effect of a cookstove intervention on carboxyhaemoglobin and forced vital capacity.

Why read on?

► Chronic respiratory morbidity in adulthood is influenced by lung health in early life—greater understanding of contributing factors is vital to promote healthy lung development during childhood.

INTRODUCTION

Non-communicable lung diseases are major global health priorities across the life course.[1 2] Asthma is the the most common chronic disease of childhood and one of the the most common chronic diseases of adulthood, affecting around 358 million people while COPD affects 174 million people, worldwide.[3]

Although most of the children and adults with these conditions live and die in low-income countries and middle-income countries (LMICs), the majority of the research into these conditions is done in high-income countries. Research is especially scarce in the LMICs of sub-Saharan Africa where limited studies suggest the prevalence of childhood asthma is increasing in urban settings, and that children with symptoms of asthma are likely to be severely symptomatic.[4 5] In adult populations, Burden of Obstructive Lung Diseases (BOLD) studies from countries in sub-Saharan Africa, including sites in urban and rural Malawi, have found a high burden of impaired lung function—particularly low forced vital capacity (FVC)[6–8]—which is concerning given the association between low FVC and mortality in other populations.[9]

In these same sub-Saharan African populations, there is widespread reliance (by around 700 million people) on inefficiently burned solid fuels for cooking, heating and lighting.[10] Studies in rural Malawi report exclusive biomass fuel use (wood, crop waste and charcoal) with households using traditional 'open-fire' cooking methods.[11] The widespread exposure of children to pollutants such carbon monoxide (CO) and particulate matter, resulting from incomplete fuel combustion, is particularly concerning. Household air pollution has been suggested as a potential contributing

factor in the development of non-communicable lung diseases in low-income countries.[12] However, the links between household air pollution exposure, new-onset asthma in children and obstructive lung disease in adults, are unclear, with controversy over the interpretation of available data.[13–17] Environmental exposures, including inhaled pollutants, during periods of lung growth and development may lead to irreversible long term deficits in adult lung function.[18 19]

In this context, the Cooking and Pneumonia Study (CAPS) was done to determine whether an intervention comprising two cleaner burning biomass-fuelled cookstoves and a solar charger would reduce the incidence of Integrated Management of Childhood Illness-defined pneumonia in children under the age of 5 years in rural Malawi compared with continuation of traditional cooking methods.[11] CAPS recruited households from village clusters in Chikhwawa between December 2013 and February 2016. The primary intention-to-treat analysis found no difference in pneumonia incidence between the two trial arms. Recently reported secondary analyses in adults from a subset of CAPS households found no difference in chronic respiratory symptoms, lung function or personal air pollution exposures between participants from the intervention and control groups.[20] That said, median exposure to fine particulate matter ($PM_{2.5}$) was 71 $\mu g/m^3$, well above WHO annual and 24 hours guidelines.

Is it not known whether the same pattern of respiratory symptoms, spirometric abnormalities and air pollution exposures would be seen in children as in adults or whether the CAPS intervention would have beneficial effects on any of these outcomes in children? In this paper we report the findings of a cross-sectional study, conducted in the same village communities as CAPS, which set out to: (1) measure the prevalence and determinants (including measured exposure to household air pollution) of non-communicable lung disease in a population representative sample of children in rural Malawi and (2) conduct an analysis comparing lung function between young children in the intervention group and those in the control group in CAPS. Some of the data have been previously presented in abstract form.[21]

METHODS

Study design

We conducted a cross-sectional study of the prevalence and determinants of non-communicable respiratory disease among children living in Chikhwawa District, Malawi.

Setting

Chikhwawa is a rural area, located in the Southern Region of Malawi on the Shire River, 50 km from the nearest city, Blantyre. The population consists largely of subsistence farmers living in village communities and is highly vulnerable to climatic shocks, having experienced flooding, crop failures and famine in recent years. Infectious diseases (malaria, pneumonia and gastroenteritis), HIV/AIDS, malnutrition and limited access to basic healthcare contribute to high childhood mortality rates, although a considerable reduction in the mortality rate for children under 5 years old has been seen in Malawi over the past 25 years.[22]

Participants

Following widespread community engagement events, children aged between 6 and 8 years, living in households that had taken part in CAPS and BOLD-Chikhwawa were identified by local community advisors and invited to participate if the child's parent/guardian gave written informed consent (or witnessed thumbprint for those unable to read and write). Exclusion criteria were current treatment for tuberculosis, current acute respiratory infection (defined as cough of <1-week duration, associated with fever and/or increased work of breathing) and other contraindications to spirometry (chest or abdominal pain, haemoptysis). We recruited all children from the study area meeting the eligibility criteria.

Procedures

Fieldworkers visited the children in the community to administer an electronic questionnaire, and assess anthropometry, lung function, and personal exposure to household air pollution. An electronic questionnaire was administered in Chichewa, the local language, detailing respiratory symptoms and potential contributing factors. Core written questions from the International Study of Asthma and Allergy in Children (ISAAC) were included, which had been forward and back-translated.[23] Height, weight and mid-upper arm circumference (MUAC) were measured according to standardised protocols. Height and weight were interpreted using the WHO 2007 child growth standards.[24] MUAC was used to assess nutritional status.[25]

Prebronchodilator and postbronchodilator spirometry was performed by BOLD centre-certified technicians, according to American Thoracic Society/European Respiratory Society (ATS/ERS) standards using an Easy On-PC Spirometer (ndd Medical Technologies; Zurich, Switzerland).[26] Regular calibration was performed according to the manufacturer's instructions. The highest forced expiratory volume in one second (FEV_1) and FVC measurements for each participant were selected (from a maximum eight attempts), before and after administration of 400 µg inhaled salbutamol, via Volumatic spacer. Reversibility was defined as ≥12% improvement between prebronchodilator and postbronchodilator FEV_1.

Spirometry over-reading was performed by two independent reviewers. Two sets of ATS/ERS standards (aged 4–6 years and aged seven and above) are relevant for the children in this study.[26 27] As the age range of our study children overlaps both sets of standards, and to maximise the use of spirometric data collected, we defined acceptable (grade C) quality as two traces within 150 mL or 10% (online supplementary table S1).

Carboxyhaemoglobin level (COHb) was measured at a single time-point using a Rad-57 pulse CO-oximeter (Masimo Corporation, California, USA). Performance verification was ensured at study outset, according to the manufacturer service manual. To assess personal CO exposure levels, children wore an EasyLog CO USB data logger (Lascar Electronics, Wiltshire, UK), for up to 48 hours, starting immediately after the field visit.

Variables

Clinical outcomes were presence or absence of symptoms, as assessed by the following questions; *Chronic cough*: defined by a positive response to both 'Does your child usually have a cough when they don't have a cold?' and 'Are there months in which they cough on most days?'; *Current wheeze*: 'Has your child had wheezing or whistling in the chest in the past 12 months?'; *Severe asthma:* current wheeze, and ≥4 attacks of wheeze, or ≥1 night per week sleep disturbance from wheeze, or wheeze affecting speech, in the past 12 months; *Shortness of breath*: a composite outcome, positive if children were reported to be breathless during normal daily activities or on minimal exertion; *Any respiratory symptom*: a composite outcome, positive if a participant was reported to have any of the previously described symptom outcomes.

Continuous FEV_1 and FVC values were used in the primary analysis. Standardised z-scores and lower limits of normal (LLN) for FEV_1, FVC and FEV_1/FVC were derived from the GLI 2012 reference equations for African-Americans, which provide race-specific and sex-specific reference values, taking into account height and age.[28]

Personal CO exposure monitoring data were not analysed if <24 hours were recorded. To allow comparison of varying lengths of recording, all data were truncated at 24 hours for the final analysis.

Potential effect modifiers included were height (cm), weight (kg), age and sex.

Study size

We calculated a sample of 600 participants (300 male, 300 female) would estimate the prevalence of non-communicable lung disease in each sex stratum with a precision (95% CI) of ±3.3 to ±5.0% (assuming a prevalence of 10%–25%). To allow for unequal sex distributions, refusals and inability to provide spirometry of acceptable quality, we aimed to recruit 1000 children.

Statistical analysis

Descriptive analysis was performed, using Student's t-test and Pearson's χ^2 to compare continuous and categorical data. For population proportions, Wald-type SEs were calculated, assuming a binomial distribution. Bivariate associations between spirometric and clinical outcomes, and variables including CO, COHb, hospital admission for respiratory illness during infancy, and CAPS allocation were explored. Harmonic regression was used to account for any possible effect of seasonality on the outcome measures. This was implemented by including sinusoidal functions (sine and cosine terms) of time with a period of 1 year. Linear multivariable regression was used to estimate the association between exposures and continuous lung function values (FEV_1 and FVC). Multivariable logistic regression models were constructed for dichotomous clinical outcomes. All models included age, sex, height and weight *a priori*, and variables with a p value <0.2 on bivariate analysis. A backward stepwise regression technique was used to develop multivariable models. An analysis was conducted to compare FEV_1, FVC and FEV_1/FVC, symptom prevalence and exposure variables between the intervention and control groups of CAPS. CO was $\log_{10}$ transformed for inclusion in linear models to ensure normality of residuals.

Analyses were conducted using R V.3.4.1 statistical software.[29]

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.

Ethical approval was given by the College of Medicine Research Ethics Committee in Malawi (reference P.07/16/1994) and Liverpool School of Tropical Medicine Research Ethics Committee in the UK (reference 16–040).

RESULTS

Between February and December 2017, we approached 886 children of whom 804 were confirmed to be eligible and were recruited (79/82 were outside the eligible age range; 3/82 guardians declined to consent). Questionnaire data were collected for all but one participant who withdrew from the study shortly after giving consent. Anthropometry, spirometry, COHb measurement and personal CO monitoring were done on 99.9% (802/803), 99.9% (802/803), 99.4% (798/803) and 99.3% (797/803) of these participants, respectively. Grade A–C prebronchodilator traces were achieved in 65% (522/802) of the children. The duration of CO monitoring was 24 and 48 hours for 91.9% (738/803) and 79.5% (638/803) children, respectively. There were 476 (260 intervention and 216 control) children from households included in CAPS (figure 1).

The mean age (SD) of participants was 7.13 (0.77) years and 417 (51.9%) participants were female. Most (700 (87.2%)) were attending primary school. The mean (SD) height-for-age and weight-for-age z-scores were −1.04 (0.90) and −1.10 (0.89), respectively. Mean (SD) MUAC was 15.98 (1.26) cm (table 1). No children met the criteria for severe or moderate acute malnutrition, but 11/789 (1.4%) children were 'at risk for acute malnutrition'.

Chronic respiratory symptoms were reported by 133 (16.6% (SE 1.3)) children, most commonly cough (8.0% (SE 1.0)), and current wheeze (7.1% (SE 0.9)) (table 1). One-fifth (159/803) of children had been admitted to hospital with respiratory

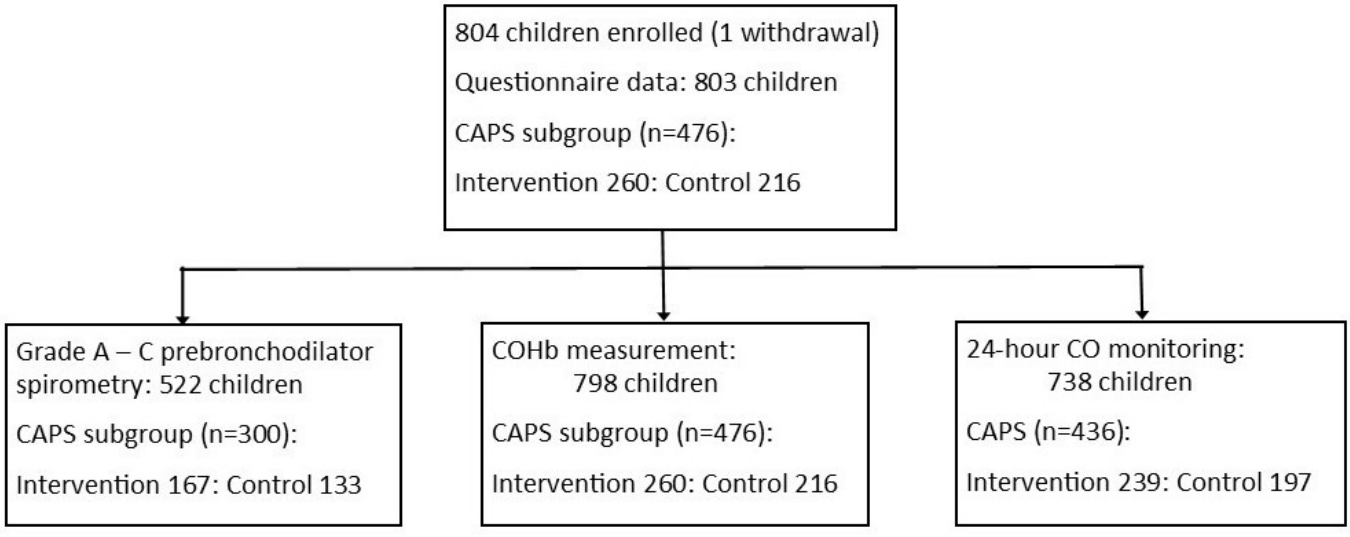

Figure 1 Participant recruitment flow diagram. CAPS, Cooking and Pneumonia Study; CO, carbon monoxide; COHb, carboxyhaemoglobin level.

Table 1 Demographics and clinical characteristics (n=803)

Female, n (%)	417 (51.9)
Age, mean (SD) years	7.13 (0.77)
School attendance, n (%)	700 (87.2)
Anthropometry	
Weight-for-age z-score, mean (SD)	−1.10 (0.89)
Height-for-age z-score, mean (SD)	−1.04 (0.90)
MUAC, mean (SD) cm*	15.98 (1.26)
Chronic respiratory symptoms	**n (%)**
Wheeze ever	97 (12.1)
Current wheeze (in the past 12 months)	57 (7.1)
Severe asthma (in the past 12 months)	31 (3.9)
Wheeze with exercise	44 (5.5)
Dry cough at night	145 (18.1)
Chronic cough	64 (8.0)
Chronic sputum production	13 (1.6)
Chronic shortness of breath	49 (6.1)
Any chronic respiratory symptom	133 (16.6)

*MUAC measurement available for 789 participants.
MUAC, mid-upper arm circumference.

symptoms in the past; on one (9.7%), two (6.1%) and three or more (4.0%) occasions. Admission for a respiratory problem during the first year of life was reported for 70 (8.7%) children. Antibiotic use for a chest problem in the last year was common, reported for 112 (13.9%) children, with 69 (8.6%) receiving these on more than one occasion. Half (54.4%) of children with current wheeze had symptoms of severe asthma, representing 3.9% of children overall. Of these, 22 (71.0%) had a previous hospital admission, and 10 (32.2%) missed school due to breathing problems. Very few (0.4%) children had previously been treated for tuberculosis, and 2.0% (6/307) of children who had been tested for HIV were HIV-positive.

Children producing grade A–C spirometry were older than those with unacceptable traces (mean age 7.23 vs 6.96 years, p<0.001); otherwise there were no significant differences in growth parameters and respiratory symptoms between the two groups (online supplementary table S2). Overall, participants had a mean (SD) FEV_1 z-score −0.48 (0.93) and mean (SD) FVC z-score of −0.30 (0.96). Children from CAPS intervention households had higher FVC z-scores than those from control households (−0.22 vs −0.44, p=0.05). Prebronchodilator spirometric abnormalities were found in 68/522 (13.0%) of children; 7.1% with low FVC and 6.3% obstruction (table 2). Postbronchodilator spirometry was attempted by 706 children, with 72% (505/706) producing grade A–C traces. Both prebronchodilator and postbronchodilator traces were available for 432 children, 26 of whom had a prebronchodilator FEV_1/FVC ratio below the LLN which was reversible in 8 (30.7%).

Personal CO monitoring showed considerable variation in exposure throughout the monitored period (figure 2). Mean exposure levels ranged from 0 to 15.1 parts per million (ppm), with a median CO exposure of 0.20 ppm (IQR 0.07–0.54). Peaks exceeding the 15 min indoor WHO guideline (81 ppm; 100 mg/m^3) were observed in 370/738 (50.1%) of participants (figure 3).[30] Median %COHb was 4.00 (IQR 1.50–6.50). 68.5% of participants had a level greater than 2%, and 6.0% greater than 10% (figure 4). We found no association between respiratory symptoms or spirometric indices and personal CO and COHb measurements in bivariate analyses and therefore these variables were not carried forward into multivariable analysis. In logistic multivariable analysis, chronic cough (OR 2.63 (95% CI 1.13 to 6.12)), current wheeze (OR 5.48 (95% CI 2.45 to 12.26)) and symptoms of severe asthma (OR 6.36 (95% CI 2.34 to 17.28)) were all associated with hospital admission during infancy (table 3). We found no association between respiratory symptoms and spirometric indices in bivariate or multivariable analysis (table 3).

In the analysis comparing intervention and control groups, we found statistically significant associations between the intervention arm and both FVC (coefficient estimate 0.04 (95% CI 0.00 to 0.07)), and COHb level (coefficient estimate −0.89 (95% CI −1.53 to 0.26) (table 4A). We found no significant differences between CAPS arms for growth parameters (table 4A) or chronic respiratory symptom rates (table 4B).

DISCUSSION

This is one of the first studies to report lung function and personal household air pollution exposure, measured concurrently in young children, and it was conducted in the context of the largest trial of a cleaner-burning cookstove intervention to date. Among children living in rural Malawi, we found that; one in six reported chronic respiratory symptoms; over half with current wheeze had severe symptoms; anthropometric and lung function parameters were generally decreased compared with global reference ranges; the majority of children had COHb levels above WHO recommended guidelines; and half of children exceeded WHO guidelines for CO exposure (100 mg/m^3), during 24 hours monitoring.[10] Overall, we found no evidence of an association between CO exposure and respiratory symptoms or lung function. However, children from CAPS intervention households had higher FVC z-scores and lower COHb levels than controls.

There are limited data regarding chronic respiratory symptoms in children from Africa, and particularly rural settings. One study from rural Senegal reported similar rates with 9% current wheeze and 5% severe asthma among children aged 5–8 years.[31] Studies from urban settings in sub-Saharan Africa, including ISAAC sites, reported rates of current wheeze in 5%–16% of young children, with symptoms of severe asthma in half of these.[4 32–34] Globally 11.5% of children aged 6–7 years have current wheeze, and 4.9% have symptoms of severe asthma; severe symptoms are seen in one-third of children with current wheeze in Europe.[4] The high rates of severe symptoms seen in low-income countries are concerning, and likely reflect multiple challenges within healthcare systems, which are better equipped to manage acute episodes relating to infectious diseases, rather than chronic non-communicable conditions. In keeping with this, recent research from Nigeria and South Africa has reported high rates of under-diagnosed and untreated asthma in schoolchildren.[35 36]

We found decreased lung function parameters in this study, comparable to values reported for community controls in a recent study exploring long-term outcomes after severe acute malnutrition, at the referral hospital in Blantyre, Malawi.[37] These lung function deficits, when compared with international reference ranges, may reflect host and environmental factors such as undernutrition, frequent respiratory infections, low birth weight, exposure to pollutants in utero and early life, which can have adverse effects on lung growth and development.[38–42] No children in this study were acutely malnourished (as defined by MUAC measurement), although other anthropometric

Table 2 Prebronchodilator lung function parameters for participants with grade A–C spirometry, including the CAPS subgroup

	Participants with A–C spirometry N=522	CAPS intervention arm N=167	CAPS control arm N=133	Intervention versus control *
FEV_1 z-score, mean (SD)	−0.48 (0.93)	−0.41 (0.92)	−0.60 (0.97)	P=0.10
FVC z-score, mean (SD)	−0.30 (0.96)	−0.22 (0.97)	−0.44 (0.98)	P=0.05
FEV_1/FVC z-score, mean (SD)	−0.38 (0.90)	−0.40 (0.91)	−0.34 (0.93)	P=0.57
FVC<LLN, n (%)	37/522 (7.1%)	11/167 (6.6%)	12/133 (9.0%)	P=0.57
Obstructive spirometry FEV_1/FVC<LLN, n (%)	33/522 (6.3%)	11/167 (6.6%)	10/133 (7.5%)	P=0.93
Abnormal spirometry (low FVC, obstruction, mixed), n (%)	68/522† (13.0%)	21/167‡ (12.6%)	22/133 (16.5%)	P=0.42

*Comparison of means using Student's t-test; comparison of proportions using Pearson's χ^2 test.
†Mixed pattern in two participants.
‡Mixed pattern in one participant.
CAPS, Cooking and Pneumonia Study; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.

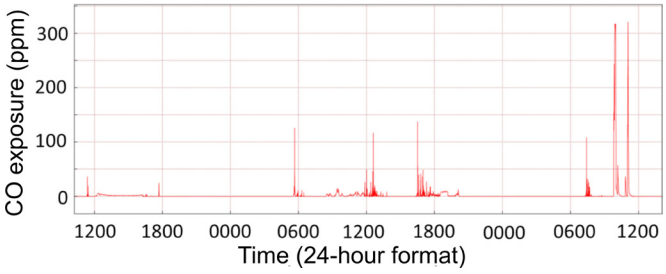

Figure 2 Example of a typical 48 hours CO monitoring trace. CO, carbon monoxide.

parameters (weight-for-age and height-for-age z-scores) were reduced compared with international standards, suggesting a level of chronic undernutrition in this community. There are limited data regarding normal lung function in healthy African paediatric populations, and consequently it is difficult to understand the clinical significance of these apparent spirometric deficits.[43] Further research is needed to describe optimal lung growth in African populations, and determine the morbidity and mortality associated with lung function abnormalities.[44]

Consistent with our previous findings in Chikhwawa, we noted exposure to high peaks of CO, reaching up to three times the WHO guidelines around cooking times, although mean and median levels were low; median CO 1.23 ppm (IQR 0.79–1.93) in adults and mean CO 1.27 ppm (SD 2.79) in younger children.[20 45] Median CO exposure levels were lower (0.20 ppm (IQR 0.07–0.54) in our older paediatric population perhaps reflecting long periods of time that children spend away from the home environment during the school day. Cookstove trial analyses exploring adult lung function as a secondary outcome have found no evidence of intervention benefit.[20 46 47] Paediatric lung function outcomes in cookstove trials are inconclusive, but signal a possible beneficial effect of the interventions. Secondary analysis from the RESPIRE trial found decreased lung growth at around 5 years of age (measured by peak expiratory flow), associated with delayed chimney stove installation, although there was no association between lung function at age five and measured personal CO exposure during the first 18 months of life.[48] The GRAPHS birth cohort in rural Ghana recently reported an association between prenatal CO exposure and infant lung function at 30 days of life, with an increased effect of exposure on female infants.[49] Cross-sectional studies from Nigeria have described decreased lung volumes (FEV_1 and FVC) and increased asthma symptoms in children with self-reported exposure to biomass cooking fuels.[36 50]

The association between CAPS intervention group and higher FVC is interesting, given the lack of evidence for an association between lung function and CO exposure or COHb level. This positive finding must be interpreted cautiously as it is the result of exploratory secondary analyses, unadjusted for multiplicity and therefore may be due to chance. However, when taken with the second signal of a potential effect, lower COHb observed in the intervention group, the results may be evidence of a genuine impact. We may have observed a benefit among our participants, who were aged 3–6 years during the CAPS trial period, in contrast to findings from adult populations, because the early childhood years represent a key period for lung development.

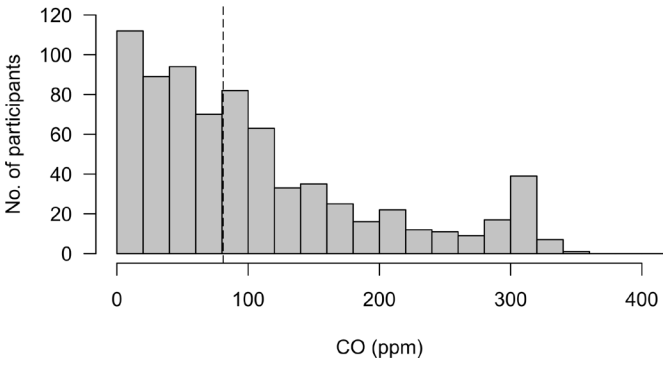

Figure 3 Maximum CO levels recorded during monitoring period for 738 participants. Dashed line represents who recommended indoor exposure guideline for a 15 min time period. CO, carbon monoxide.

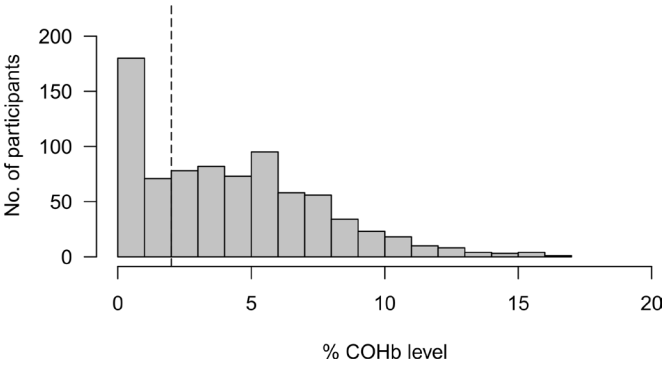

Figure 4 Percentage of COHb level for 798 participants. Dashed line represents the WHO COHb guideline. COHb, carboxyhaemoglobin level.

Table 3 OR (95% CI) for chronic respiratory symptoms estimated by multivariable logistic regression (n=522)

	Cough	Current wheeze	Severe asthma	Shortness of breath
Age (years)	0.72 (0.48 to 1.06)	0.55 (0.31 to 0.96)*	–	–
Sex	–	–	–	–
Height (cm)	–	1.07 (0.99 to 1.17)	1.18 (1.04 to 1.35)*	1.06 (0.98 to 1.14)
Weight (kg)	–	–	0.72 (0.54 to 0.94)*	–
Admission during infancy	2.63 (1.13 to 6.12)*	5.48 (2.45 to 12.26)†	6.36 (2.34 to 17.28)†	–
FEV_1 (l)‡	–	0.14 (0.01 to 1.72)	0.04 (0.00 to 1.09)	1.24 (0.01 to 1.17)

*Significant at 0.05 level.
†Significant at 0.001 level.
‡Prebronchodilator FEV_1.

FEV_1, forced expiratory volume in one second.

There is rapid alveolar expansion and resulting lung growth during the first 2 years of life, which stabilises around 8 years of age.[51] Alveolar number is reflected by FVC in childhood and so it is biologically plausible that we might see improved lung function in children from the intervention arm; the apparent difference of 70 mL in mean FVC between CAPS groups represents approximately 6% of a child's lung volume. Furthermore, young children have increased susceptibility to air pollutants, exhibiting increased deposition of particles in the lung, due to physiological and anatomical factors.[52] CO exposure measures do not appear to be associated with lung function or respiratory symptoms—perhaps CO is an inadequate proxy for other pollutants of interest, such as $PM_{2.5}$ and nitrogen dioxide. Our previous air pollution monitoring work in Chikhwawa has demonstrated that monitored CO exposure correlates weakly with COHb, $PM_{2.5}$ exposure, and measured black carbon in airway cells from induced sputum.[20 45 53]

This study was conducted in the context of the largest cookstove intervention trial to date—a major strength enabling us to assess the effect of a cookstove intervention on childhood spirometry and air pollution exposure outcomes. Other strengths include high participation rates for spirometry and

Table 4A CAPS secondary trial analyses: mean or median values, with linear model coefficient estimates (95% CI) for continuous outcomes

	Intervention	Control	Intervention versus control	P value
FEV_1, mean (SD) L*	1.02 (0.18)	0.97 (0.19)	0.02 (–0.01 to 0.06)	0.135
FVC, mean (SD) L*	1.16 (0.21)	1.09 (0.21)	0.04 (0.00 to 0.07)	0.033
FEV_1/FVC, mean (SD) *	0.88 (0.06)	0.89 (0.06)	–0.01 (–0.02 to 0.01)	0.411
%COHb, median (IQR)†‡	3.50 (1.00 to 6.00)	4.85 (2.00 to 7.00)	–0.89 (–1.53 to –0.26)	0.006
Mean CO ppm, median (IQR)§‡¶**	0.18 (0.05 to 0.55)	0.20 (0.08 to 0.52)	0.03 (–0.35 to 0.42)	0.857
Weight-for-age z-score, mean (SD)†	–1.20 (0.89)	–1.06 (0.85)	–0.13 (–0.29 to 0.02)	0.096
Height-for-age z-score, mean (SD)†	–1.10 (0.84)	–1.06 (0.93)	–0.04 (–0.20 to 0.12)	0.624
MUAC, mean (SD) cm††	15.92 (1.29)	15.94 (1.30)	–0.02 (–0.26 to 0.21)	0.846

*Spirometry data for 300 participants; 167 intervention, 133 control. FEV_1, FVC and FEV_1/FVC adjusted for age, sex, height and weight in regression model.
†COHb, height and weight data for 476 participants; 260 intervention, 216 control.
‡Adjusted for seasonality in linear regression model.
§24 hours CO monitoring for 436 participants; 239 intervention, 197 control.
¶Log_{10} CO values used in linear regression model.
**Mean exposure was estimated over the monitoring period per individual, the median of these values (and IQR) is presented for the study population.
††MUAC for 466 participants; 260 intervention, 206 control.
CO, carbon monoxide; COHb, carboxyhaemoglobin level; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; MUAC, mid-upper arm circumference.

Table 4B CAPS secondary trial analyses: proportions and OR (95% CI) for symptom outcomes (n=476)

	Intervention n=260	Control n=216	Intervention versus control	P value
Cough, n (%)	30 (7.7%)	18 (8.3%)	0.92 (0.47 to 1.78)	0.797
Current wheeze, n (%)	19 (7.3%)	17 (7.9%)	0.92 (0.47 to 1.82)	0.817
Severe asthma, n (%)	11 (4.2%)	10 (4.6%)	0.91 (0.38 to 2.19)	0.833
Shortness of breath, n (%)	13 (5.0%)	14 (6.5%)	0.75 (0.34 to 1.63)	0.471
Any respiratory symptom, n (%)	37 (14.2%)	40 (18.5%)	0.72 (0.44 to 1.18)	0.193

CO exposure monitoring, and good quality spirometry in a representative sample of children, despite the highly challenging research environment of a rural area in a low-income country. We achieved our sample size, even though field work was disrupted by vampirism hysteria in the community. We acknowledge limitations to our study including that personal monitoring of CO for 48 hours provides only a snapshot of exposure to a single pollutant. There are substantial limitations to the methods currently available for monitoring personal exposure to other pollutants in this young age group; the Lascar CO-monitoring device represents one of the best options available, at present. Monitoring during a 48 hours exposure period may not describe individual variation in daily and seasonal routines but reflected a compromise in terms of feasibility and acceptability in this large study population. Questionnaire data may have been subject to recall bias, with limited information on contributing factors such as birth weight, gestation at birth, HIV-status and exposure to passive smoking.

In conclusion, the substantial burden of chronic respiratory symptoms, abnormal spirometry and air pollution exposures in children in rural Malawi is concerning and calls for strategies to maximise healthy lung development and to effectively manage chronic respiratory conditions. To achieve this, research will be needed to develop ways to increase awareness of non-communicable lung diseases, such as asthma, at a community level to inform healthcare seeking behaviours and ensure access to appropriately trained healthcare providers and effective long-term treatment such as inhaled medication. Our finding of a potential beneficial effect of a cleaner burning biomass-fuelled cookstove on lung function (FVC) calls for further research into clean-air initiatives, tackling multiple sources of air pollution in a community-wide approach to promote lung health in children.

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Contributors Design: KM, JG, SR. Acquisition of data: SR, RN, AN, FM, KM. Analysis of data: SR, RN, CJ, JG, KM. Interpretation of data: SR, RN, CJ, JRB, JG, 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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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethical approval was given by the College of Medicine Research Ethics Committee in Malawi (reference P.07/16/1994) and Liverpool School of Tropical Medicine Research Ethics Committee in the UK (reference 16-040).

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ORIGINAL RESEARCH

Non-communicable respiratory disease and air pollution exposure in Malawi: a prospective cohort study

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ABSTRACT

Rationale There are no population-based studies from sub-Saharan Africa describing longitudinal lung function in adults.

Objectives To explore the lung function trajectories and their determinants, including the effects of air pollution exposures and the cleaner-burning biomass-fuelled cookstove intervention of the Cooking and Pneumonia Study (CAPS), in adults living in rural Malawi.

Methods We assessed respiratory symptoms and exposures, spirometry and measured 48-hour personal exposure to fine particulate matter ($PM_{2.5}$) and carbon monoxide (CO), on three occasions over 3 years. Longitudinal data were analysed using mixed-effects modelling by maximum likelihood estimation.

Measurements and main results We recruited 1481 adults, mean (SD) age 43.8 (17.8) years, including 523 participants from CAPS households (271 intervention; 252 controls), and collected multiple spirometry and air pollution measurements for 654 (44%) and 929 (63%), respectively. Compared with Global Lung Function Initiative African-American reference ranges, mean (SD) FEV_1 (forced expiratory volume in 1 s) and FVC (forced vital capacity) z-scores were −0.38 (1.14) and −0.19 (1.09). FEV_1 and FVC were determined by age, sex, height, previous TB and body mass index, with FEV_1 declining by 30.9 mL/year (95% CI: 21.6 to 40.1) and FVC by 38.3 mL/year (95% CI: 28.5 to 48.1). There was decreased exposure to $PM_{2.5}$ in those with access to a cookstove but no effect on lung function.

Conclusions We did not observe accelerated lung function decline in this cohort of Malawian adults, compared with that reported in healthy, non-smoking populations from high-income countries; this suggests that the lung function deficits we measured in adulthood may have origins in early life.

Key messages

What is the key question?

► Are the low lung volumes previously reported in adults from Malawi a result of impaired lung development in early life or accelerated lung function decline in adulthood or both, and does biomass smoke exposure influence the rate of decline in the same way as tobacco smoke exposure?

What is the bottom line?

► In an adult population with high biomass smoke exposure, we found rates of lung function decline comparable with healthy non-smokers in high-income countries and lung function z-scores consistent with those reported in children from the same rural Malawian community.

Why read on?

► We report the first longitudinal lung function data from a population-representative cohort in sub-Saharan Africa: the results suggest that exposure to biomass fuel smoke may be less harmful than exposure to tobacco smoke or traffic-related air pollution, as reported in high-income settings.

INTRODUCTION

Non-communicable respiratory diseases including chronic obstructive pulmonary disease (COPD) and asthma are a growing global concern, particularly in low-income and middle-income countries.[1–3] Air pollution, including exposure to tobacco smoke, outdoor and household air pollutants, and occupational exposure to dust and fumes, is considered a major risk factor for non-communicable respiratory disease development and exacerbations.[1 4] However, conflicting findings from recent studies have cast uncertainty over the specific role of household air pollution in COPD development.[5 6] Approximately 3 billion people worldwide rely on highly polluting biomass fuels for cooking, heating and lighting.[7] It is therefore a global public health priority to better understand the impact of household air pollution on non-communicable respiratory disease morbidity and mortality.

The lung function trajectories of adults from sub-Saharan Africa (sSA) are largely undescribed; limited published data relate to cohorts from South Africa with HIV-infection and occupational silica dust exposure.[8 9] There are no data from population-representative cohorts in sSA; it is not known whether adults exposed to biomass-related air pollution would experience accelerated age-related decline in lung function and therefore an increased risk of developing obstructive airways diseases as occurs in those exposed to tobacco smoke.[10 11]

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The cross-sectional BOLD (Burden of Obstructive Lung Disease) study, conducted in urban Blantyre, Malawi found unexpectedly high rates of decreased forced vital capacity (FVC) and high levels of self-reported exposure to biomass smoke.[12] The finding of a high burden of low FVC was concerning given the association between this and increased mortality.[13] To further explore this phenomenon, we did a second study in rural Chikhwawa, Malawi (entitled BOLD-Chikhwawa) with the same protocol as the Blantyre BOLD study, but with the addition of measurement of personal exposure to air pollutants: carbon monoxide (CO) and fine particulate matter <2.5 µm ($PM_{2.5}$).[14] We found comparably high rates of spirometric abnormalities, with decreased FVC seen in 35% of participants, but no association between spirometric outcomes and exposure to CO or $PM_{2.5}$ despite high levels of air pollution. Participants were from village communities which also participated in the Cooking and Pneumonia Study (CAPS), a cluster randomised trial of a cleaner-burning biomass-fuelled cookstove.[15] Secondary analysis of adults from a subset of CAPS households found no difference in respiratory symptoms, lung function or personal air pollution exposures between intervention and control groups, but these analyses were done using cross-sectional data that were collected only a short time after introduction of the intervention—it is not known whether the rate of decline in lung function over time would be different between the trial arms.[14]

In this paper, we report the findings of lung function and personal air pollutant exposure monitoring during 3 years of follow-up for the BOLD-Chikhwawa cohort, to explore the determinants of lung function trajectories, including the effect of the CAPS cookstove intervention, in adults living in rural Malawi.

METHODS

Setting

Chikhwawa is a rural district, approximately 50 km south of Blantyre, on the Shire River valley. During the study period, this district experienced severe flooding and crop failures. CAPS recruited children aged <4.5 years in Chikhwawa between December 2013 and August 2015; intervention households received two cleaner-burning biomass-fuelled cookstoves, a solar panel to charge the stove-fan battery and user training at the time of randomisation. Those in the control arm continued using traditional cooking methods, mostly open fires, but received cookstoves at the end of the CAPS follow-up in May 2016.

BOLD-Chikhwawa was a separate study, recruiting adults from the same village communities as CAPS: not all BOLD-Chikhwawa participants were enrolled in CAPS. Figure 1 shows the timeline of CAPS and BOLD-Chikhwawa activities.

Participants

Age-stratified and gender-stratified population-representative sample of adults from 50 villages in Chikhwawa was taken as previously described.[14] Written informed consent (or witnessed thumbprint) was obtained, with the information provided in the local language, Chichewa.

Procedures

Fieldworkers conducted follow-up visits in the community, approximately 1 and 2 years after enrolment, according to BOLD study standardised operating procedures, to collect questionnaires, spirometry and personal air pollution exposure data.[16] Fieldworkers administered an abbreviated version of the BOLD study questionnaire in Chichewa, and measured height and weight.

BOLD Centre-certified fieldworkers conducted spirometry according to European Respiratory Society(ERS)/American Thoracic Society (ATS) standards using an EasyOne Spirometer (ndd Medical Technologies; Zurich, Switzerland), before and after administration of 200 µg of Salbutamol via Volumatic spacer.[17] Spirometry overreading was performed by an independent technician, according to the BOLD criteria for acceptability and repeatability.

After completing the questionnaire and spirometry assessment, participants were given an Indoor Air Pollution (IAP) 5000 Series Monitor (Aprovecho Research Centre, Oregon, USA) which they were instructed to wear in a small backpack during the day and to keep beside their sleeping mat at night, to estimate personal exposure to $PM_{2.5}$ and CO over a 48-hour period. These monitors continuously sample air from the breathing zone, and $PM_{2.5}$ and CO are measured using a light-scattering photometer and electrochemical cell CO sensor, respectively. Fieldworkers encouraged compliance with personal exposure monitoring during frequent community visits. IAP traces with outlying $PM_{2.5}$ or CO values (extremely high or low) were visually inspected for expected daily variation in exposure: traces without variability, suggesting that backpacks had not been worn, were excluded from the analysis.

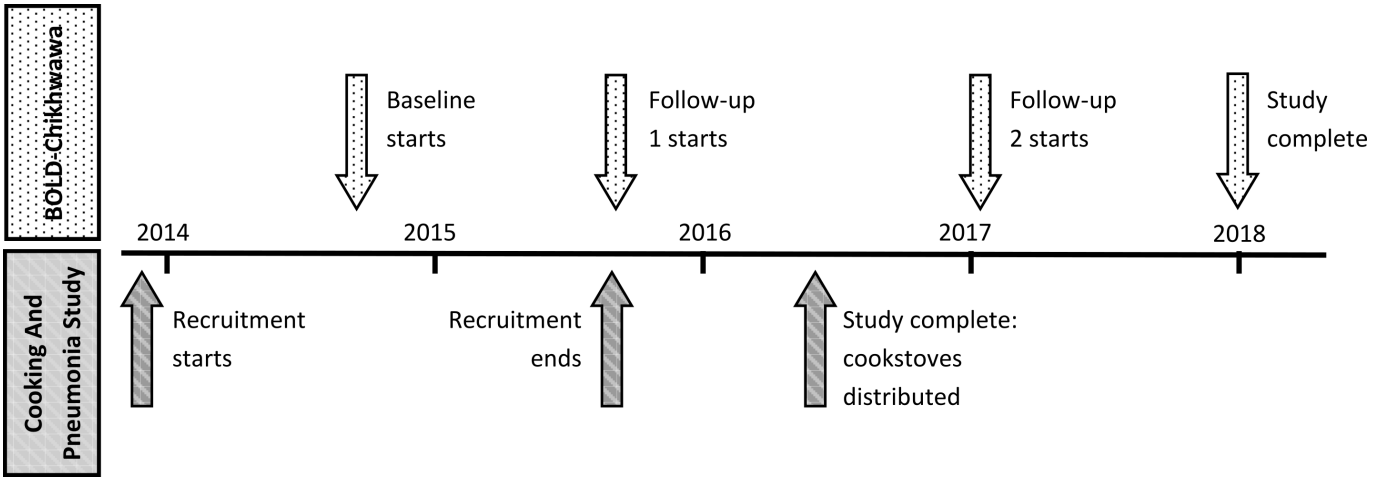

Figure 1 Timeline showing CAPS and BOLD-Chikhwawa activities. BOLD, Burden of Obstructive Lung Disease; CAPS, Cooking and Pneumonia Study.

Table 1 Respiratory symptoms and exposures reported by participants at baseline, first and second follow-up.

	% (95% CI)		
	Baseline (n=1481)	Follow-up 1 (n=1090)	Follow-up 2 (n=989)
Respiratory symptoms			
Cough: Do you usually cough when you do not have a cold?	11.1 (9.6 to 12.9)	10.1 (8.4 to 12.0)	25.3 (22.6 to 28.1)
Sputum: Do you usually bring up phlegm from your chest when you do not have a cold?	2.6 (1.8 to 3.5)	4.9 (3.7 to 6.3)	11.1 (9.2 to 13.2)
Wheeze: Have you had wheezing/ whistling in your chest in the last 12 months, in the absence of a cold?	1.6 (1.0 to 2.3)	1.7 (1.0 to 2.6)	3.0 (2.1 to 4.3)
MRC dyspnoea II: Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill?	1.6 (1.0 to 2.3)	6.6 (5.2 to 8.2)	11.8 (9.9 to 14.0)
Functional limitation: Have breathing problems interfered with your usual daily activities?	2.9 (2.1 to 3.9)	5.7 (4.4 to 7.2)	7.1 (5.6 to 8.9)
Any respiratory symptom (any of the above five symptoms)	13.6 (11.9 to 15.4)	19.6 (17.3 to 22.1)	36.2 (33.3 to 39.4)
Self-reported exposures			
Current smoker	13.9 (12.2 to 15.8)	11.6 (9.7 to 13.6)	12.9 (10.9 to 15.2)
Previous TB	3.2 (2.3 to 4.2)	3.0 (2.1 to 4.2)	2.6 (1.7 to 3.8)

TB, tuberculosis.

Variables

Clinical outcomes were assessed by the questions detailed in table 1. Raw forced expiratory volume in 1 s (FEV_1) and FVC values were used as continuous variables in the longitudinal analysis. Lung function parameters were compared with age, sex and height-standardised global lung initiative (GLI) reference ranges for African-Americans and NHANES III reference ranges for Caucasians and African-Americans.[18 19] Restriction was defined as FVC below the lower limit of normal (LLN), and obstruction as FEV_1/FVC ratio below the LLN; values below the fifth centile in a healthy, non-smoking reference population.

Exposures included estimated personal exposure to $PM_{2.5}$ and CO, and questionnaire assessment of smoking status and previous tuberculosis. At baseline, first and second follow-up, participants were classed as having access to a cookstove if their household had been given a cleaner-burning biomass-fuelled cookstove by the CAPS study team prior to data collection.

Baseline $PM_{2.5}$ and CO levels were zeroed at the 0.1th percentile of values obtained during each monitoring period. Observations were included if >24 hours were recorded, with recording truncated into 24-hour periods to reflect daily variation in personal exposure patterns, and only full 24-hour periods analysed. Log mean 24-hour $PM_{2.5}$ and CO estimates were used for mixed-effects modelling.

Potential effect modifiers: body mass index (BMI) and/or height and weight, age, years of education and sex, were evaluated as fixed covariates in the FEV_1 and FVC linear mixed-effects models.

Study size

A total of 3000 adults were initially invited to enrol in the baseline BOLD-Chikhwawa cohort. Participants were followed up if they had completed a baseline questionnaire (1481 participants) and were included in the longitudinal lung function analysis if they had at least two valid spirometry assessments during the study period.

Statistical methods

Descriptive analysis was performed, with the Student *t* test and Pearson's χ^2 to compare continuous and categorical data.

Participants with incomplete data (lost-to-follow-up or failing to complete spirometry) were compared with those with complete data using χ^2 and Student *t* tests. Positive associations ($p<0.2$) on bivariate analysis were explored in multivariable logistic regression.

Two separate mixed-effects models were developed for the analysis of repeated exposure and lung function outcomes. In the log-linear exposure models, repeated estimates (mean 24 hours CO and $PM_{2.5}$) from individuals were accounted for using an individual-level random effect, with an additional random-effect accounting for clustering of 24-hour measurements within 48-hour monitoring periods. Fixed-effect covariates were selected sequentially to determine the optimum model fit by likelihood ratio testing under maximum likelihood estimation (MLE), with the calculation of parameter estimates, standard errors and p values (see the online supplementary tables S2 and S3). Harmonic terms were included in the exposure models to account for any possible effect of seasonality on the outcome measures. This was implemented by including sinusoidal functions (sine and cosine terms) of time with a period of 1 year.

Longitudinal lung function (FEV_1 and FVC) linear models included the fitted CO and $PM_{2.5}$ values from the exposure model as fixed covariates; an average value was calculated where participants had multiple periods of exposure monitoring. Fixed-effect covariates were sequentially assessed by likelihood ratio testing under MLE (see the online supplementary tables S4 and S5), with interaction terms to explore the change in lung function over time. The final regression equations used in the exposure and lung function analysis are included in the online supplementary text S1.

Analyses were conducted using R V.3.4.1 statistical software.

RESULTS

Between August 2014 and July 2015, 1481 adults were enrolled in the study at baseline and followed up on two subsequent occasions.[14] Three-quarters (75%, n=1090) were reassessed during the first follow-up period (August 2015–November 2016) and two-thirds (67%, n=989) during the second follow-up period (January 2017–November 2017) with data collected as shown in figure 2. Demographic data for participants with or without a questionnaire, spirometry or exposure monitoring are shown in the online supplementary table S1. Participants completing the second follow-up visit were more likely to be women (OR (95% CI): 1.88 (1.50 to 2.37), and to have spent fewer years in education (OR (95% CI): 0.96 (0.93 to 0.99)).

Spirometry was attempted by 950/1481 (64%), 628/1090 (58%) and 571/989 (58%), and personal air pollution exposure monitoring completed for 1029/1481 (69%), 830/1090 (76%) and 811/989 (82%) at baseline, first and second follow-ups, respectively (figure 2). Multiple spirometry measurements were available for 654/1481 (44%) of participants, whereas 413 (28%) had only one spirometry measurement and 413 (28%) had none. Personal air pollution exposure was estimated on more than one occasion for 929/1481 (63%) of participants, whereas 401 (27%) had only one episode of monitoring and 151 (10%) had none.

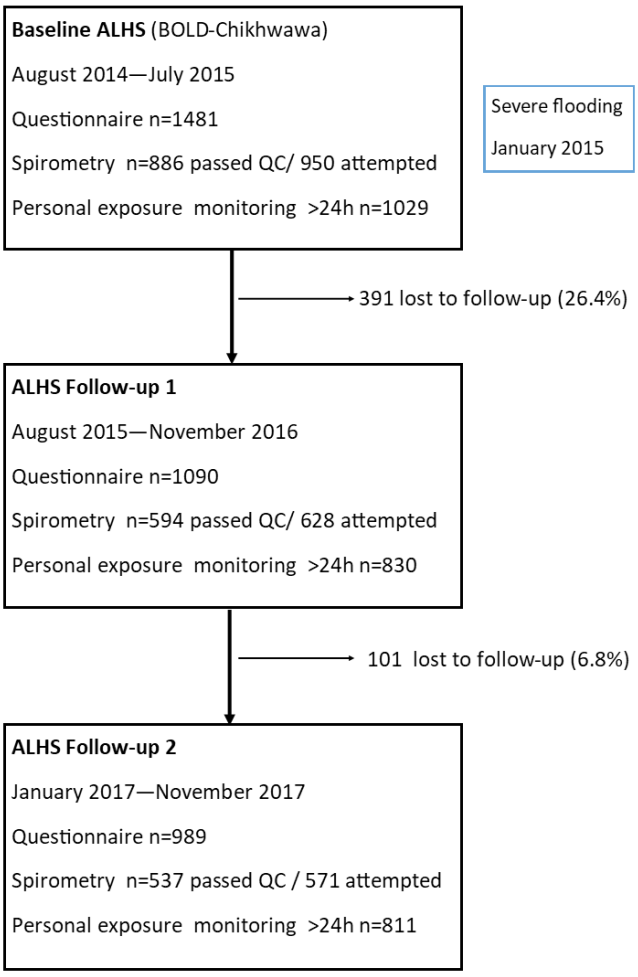

Figure 2 Participant flow diagram.

At baseline, the cohort included 424 participants from CAPS households: this rose to 523 participants (271 from intervention and 252 from control households) as CAPS continued to recruit until August 2015.

The baseline demographics of the cohort have been previously reported.[14] In brief, at baseline the mean (SD) age of participants was 43.8 (17.8) years, 57% were women and all households (99.8%) used biomass fuels for cooking. One third had never attended school and half had not been educated beyond the primary school level.

The frequency of reported respiratory symptoms increased greatly over the course of the study (table 1): overall 13.6% (95% CI: 11.9 to 15.4) of participants reported respiratory symptoms at baseline compared with 36.2% (95% CI: 33.3 to 39.4) at the final follow-up. Self-reported rates of smoking and TB did not change over time; current smoking was reported by 13.9% and 12.9%, and previous TB infection reported by 3.2% and 2.6%, at the baseline and final follow-up, respectively.

Personal exposure monitoring

A total of 1768 personal exposure monitoring episodes lasted >48 hours, and a further 902 lasted between 24 and 48 hours. Within episodes of >48 hours, there was fair correlation between the first and second 24-hour periods, for both $PM_{2.5}$ (adjusted R^2=0.68) and CO (adjusted R^2=0.59). Correlation between exposures to the two air pollutant measures (mean $PM_{2.5}$ and CO), analysed for a total of 4438 24 hours monitoring periods was poor (adjusted R^2=0.027).

Table 2 Estimated risk ratios and 95% CIs for fixed-effects covariates included in final air pollutant exposure log-linear mixed-effect models

	$PM_{2.5}$ (µg/m^3)	CO (ppm)
Sex	1.27 (1.13 to 1.42)	1.60 (1.51 to 1.72)
Current smoking	–	1.22 (1.12 to 1.34)
Seasonality: cosine function	–	0.85 (0.81 to 0.89)
Seasonality: sine function	–	0.99 (0.96 to 1.03)
Access to cookstove	0.85 (0.75 to 0.97)	–

CO, carbon monoxide; $PM_{2.5}$, fine particulate matter.

Overall, the 24 hours median personal $PM_{2.5}$ and CO exposures were 77.0 µg/m^3 (IQR, 42.8–153.1) and 1.27 ppm (IQR, 0.79–2.05), respectively. Personal $PM_{2.5}$ (median (IQR)) was 71.7 µg/m^3 (42.8–128.0), 84.6 µg/m^3 (45.9–175.7) and 75.9 µg/m^3 (40.1–176.4) at baseline, first and second follow-up, respectively. Personal CO exposure (median (IQR)) was 1.26 (0.79–2.07) ppm, 1.33 (0.81–2.22) ppm and 1.22 (0.75–1.90) ppm, at baseline, first and second follow-up, respectively.

In total, 4377 24-hour monitoring periods with complete covariate data from 1304 individuals were included in mixed-effects exposure models, with CO and $PM_{2.5}$ as the response variables. In the final CO model, we found strong evidence that female sex, current smoking status and seasonality were associated with the CO level (tables 2 and online supplementary table S2). In the final $PM_{2.5}$ model, female sex was associated with increased $PM_{2.5}$ and access to a cookstove with decreased $PM_{2.5}$ (risk ratio 0.85; 95% CI: 0.75 to 0.97) (tables 2 and online supplementary table S3).

Spirometry

Of those attempting spirometry, ERS/ATS standards were achieved by 886/950 (93.3%), 594/628 (94.6%) and 537/571 (94.0%) at baseline, first and second follow-up visits, respectively (figure 2). On bivariate analysis, factors associated with failing to complete spirometry were: older age, lower BMI, female sex, current smoking, cough or any respiratory symptoms. In logistic multivariable analysis, participants who were women (OR (95% CI), 0.52 (0.39–0.71)), older (OR (95% CI), 0.97 (0.96–0.98)) or with a lower BMI (OR (95% CI), 1.09 (1.04–1.14)) were significantly less likely to complete spirometry. Participants with longitudinal spirometry data had reduced lung function at baseline, compared with those who performed spirometry on only one occasion: mean (SD) FEV z-score −0.48 (1.03) vs -0.22 (1.28), mean (SD) FVC z-score −0.33 (1.01) vs 0.03 (1.19), respectively.

Best post-bronchodilator traces were analysed for 1068 participants who completed at least one spirometry session to ERS/ATS standards. Overall, mean (SD) FEV_1 and FVC were 2.55 (0.64) L and 3.16 (0.73) L, respectively, with a mean (SD) FEV_1/FVC ratio of 0.80 (0.09) (table 3). When compared with GLI African-American reference ranges, mean (SD) FEV_1, FVC and FEV_1/FVC ratio z-scores were −0.38 (1.14), −0.19 (1.09) and −0.37 (1.04), respectively, with spirometric obstruction seen in 11.2% (95% CI: 9.4% to 13.2%) and low FVC in 8.1% (95% CI: 6.5% to 9.9%). Rates of obstruction were similar when NHANES Caucasian reference ranges were used (11.5% (95% CI: 9.6% to 13.5%)), but considerably more—approximately 50%—of

Table 3 Best post-bronchodilator spirometry values* and classification by GLI and NHANES reference ranges for 1068 participants

Spirometry value		
Raw	Mean (SD) FEV_1, L	2.55 (0.64)
	Mean (SD) FVC, L	3.16 (0.73)
	Mean (SD) FEV_1/FVC ratio	0.80 (0.09)
Z-scores†	Mean (SD) FEV_1 z-score	−0.38 (1.14)
	Mean (SD) FVC z-score	−0.19 (1.09)
	Mean (SD) FEV_1/FVC ratio z-score	−0.37 (1.04)
Classification		**% of Population (95% CI)**
Obstruction	FEV_1/FVC<LLN GLI African-American	11.2 (9.4 to 13.2)
	FEV_1/FVC<LLN NHANES African-American	11.5 (9.6 to 13.5)
	FEV_1/FVC<LLN NHANES Caucasian	9.8 (8.1 to 11.7)
Restriction	FVC <LLN GLI African-American	8.1 (6.5 to 9.9)
	FVC <LLN NHANES African-American	7.7 (6.2 to 9.5)
	FVC <LLN NHANES Caucasian	49.7 (46.7 to 52.8)

†Z-scores calculated using GLI African-American reference ranges.
*For participants with spirometry measured at more than one time point, the best FEV_1 and FVC values were analysed.
FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GLI, global lung initiative; LLN, lower limit of normal.

participants were classified as having a low FVC (49.7% (95% CI: 46.7% to 52.8%).

Overall, the annual rate of lung function decline was 30.9ml (95% CI: 21.6 to 40.1) for FEV_1 and 38.3ml (95% CI: 28.5 to 48.1) for FVC. Age, sex, height, previous TB infection and BMI were included in the final mixed-effects models as significant fixed-effect covariates for FEV_1 and FVC (all $p<0.001$, online supplementary table S4 and S5), although they did not affect the rate of lung function decline. Current smoking, access to a cookstove, PM2.5 and CO exposure levels did not significantly improve either model. Decreased FEV_1 and FVC were associated with increasing age, female sex, previous TB infection and decreased height and BMI (table 4).

DISCUSSION

This is the first prospective cohort study to report longitudinal lung function and personal exposure to air pollution in an sSA population. The main findings were that: FEV_1 and FVC were determined by age, sex, height, previous TB and BMI, whereas there was no evidence of accelerated lung function decline (30.9 mL FEV_1 and 38.3 mL FVC annual decrease) as might have been expected in this population compared with the natural age-related decline reported in populations from Europe and the USA.[10] Mean (SD) FEV_1 and FVC z-scores (−0.38 (1.14) and −0.19 (1.09)) were comparable with those previously reported for children from this community adding to evidence that spirometric abnormalities in adults have their origins in early life.[20] Lung function was not associated with exposure to CO, $PM_{2.5}$ or access to a cookstove. Estimated CO and $PM_{2.5}$ correlated poorly and were associated with different covariates. Exposure to $PM_{2.5}$ was increased in women and decreased by a factor of 0.85 (95% CI: 0.75 to 0.97) in those with access to a cookstove. Exposure to CO was increased in women and current smokers and showed a seasonal trend.

Table 4 Parameter estimates for multiple fixed-effects covariates included in final FEV_1 and FVC linear mixed-effect models*

	FEV_1 (mL)		FVC (mL)	
	Estimate	**95% CI**	**Estimate**	**95% CI**
Time (years)	−30.9	−40.1 to 21.6	−38.3	−48.1 to −28.5
Age (years)	−18.7	−20.4 to −16.9	−11.0	−13.0 to −9.1
Sex (female)	−500.1	−566.6 to −433.6	−678.0	−751.4 to −604.7
Height (cm)	23.6	19.9 to 27.3	32.8	28.7 to 36.9
Previous TB (yes)	−404.9	−539.7 to −230.2	−334.2	−526.6 to −141.8
BMI	21.9	13.8 to 30.0	21.3	12.4 to 30.2

*Models include FEV_1 and FVC data from 950 individuals, including 654 with two or more lung function measurements
BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; TB, tuberculosis.

We did not find evidence of accelerated lung function decline despite exposure to high levels of $PM_{2.5}$. Previous studies exploring the impact of $PM_{2.5}$ on lung function in high-income settings have focused on $PM_{2.5}$ from ambient air pollution, particularly traffic-related air pollution (TRAP). Faster lung function decline was associated with increasing $PM_{2.5}$ in longitudinal cohorts from the USA and Taiwan, the effects of other pollutants were not reported.[21 22] A large multicentre metanalysis from the European ESCAPE cohorts did not find an association between air pollution and lung function decline but noted that NO_2 was negatively associated with lung function.[23] It is possible that the emissions from incomplete biomass combustion are less harmful to the airways than the many constituents (including nitrogen oxides) of TRAP.

Previous work from Malawi has reported lung function relative to NHANES III Caucasian reference values to facilitate comparison with other BOLD studies.[12 14] In this analysis, we have additionally compared our data with African-American reference ranges (NHANES and GLI). The prevalence of reduced FVC varies greatly depending on which reference equation is used.[24] The prognostic significance of markedly different predicted values in different ethnic populations is unclear.[25] Reduced FVC is seen in restrictive lung disease, however a more detailed assessment of total lung capacity by plethysmography is needed to further characterise the pattern of lung defect seen in African populations.

The use of GLI reference ranges permitted direct comparison with spirometry data from children living in the same community. We recently reported lung function for children aged 6–8 years, living in Chikhwawa; FEV_1, FVC and FEV_1/FVC ratio z-scores were −0.48 (0.93),−0.30 (0.96) and −0.38 (0.90), respectively, compared with GLI African-American reference ranges.[20] The finding of similar z-scores in both the children and adults living in this community suggests that factors which influence lung growth and development act in early childhood before 6 years of age, perhaps even starting in-utero.

We found an increase in self-reported respiratory symptoms over the 3-year follow-up period but no changes in exposures (self-reported TB or smoking status, or measured $PM_{2.5}$ or CO). We speculate this is due to changes in reporting behaviour rather than a true change in symptom prevalence. During the CAPS period, the local community were exposed to messages about the health impact of air pollution and may have become sensitised to the issues of clean air and respiratory health. Participants became familiar with the same questions asked on repeated occasions: this may have led to a positive reporting bias. Alternatively, responses at baseline may have underreported symptom

prevalence: a community survey in two rural districts in Central Malawi reported chronic respiratory symptoms in 22.5% of the population.[26]

Previous cookstove intervention trials have explored lung function in adult women only.[27 28] The RESPIRE randomised controlled trial in Guatemala reported a reduction in 48-hour personal CO exposure in the intervention group using a plancha woodstove but no effect on women's lung function at 12–18 months in an intention-to-treat analysis.[28] A subsequent exposure–response analysis did find a significantly decreased rate of decline with decreased exposure to CO.[29] The use of a Patsari stove in rural Mexico was associated with a significantly decreased rate of lung function (FEV_1) decline in women compared with those cooking on open fires (31 vs 62 mL), over 1 year of follow-up, but this effect was not observed on intention-to-treat analysis.[27] This decrease in decline is comparable with that reported among ex-smokers, in the first year after quitting; their FEV_1 trajectory showed half the rate of annual decline compared with those who continued to smoke ((mean±SD) 31±48 vs 62±55 mL).[30] Our finding of FEV_1 annual decline of 30.9 mL is consistent with the ranges seen in non-smokers from various studies.[11]

Our findings would suggest that low lung volumes seen in Malawian adults are not a result of accelerated decline in lung function, but more likely a failure to reach maximal lung volumes in early adulthood, either due to low lung function at birth or suboptimal lung growth during early childhood. Low birth weight and prematurity are of particular relevance in Malawi; the country has the highest rate of preterm birth worldwide, and intrauterine growth restriction, in both term and preterm infants, is common in low-income countries due to maternal factors including young maternal age, short-interpregnancy intervals and congenital infections.[31 32] Adverse effects of prenatal exposure to household air pollution on infant lung function have been suggested by the recent GRAPHS trial in Ghana.[33] The adverse effect of early respiratory infections on lung health in adulthood has long been recognised; such infections are common in ssA, particularly during the first year of life.[34 35]

Several studies have used CO levels as a proxy for particulate matter, which is challenging to measure in the field in low-resource settings. However, respirable particulate matter ≤2.5 µm ($PM_{2.5}$) can reach the alveolar level in the lungs and is of greater interest when considering the adverse respiratory effects of air pollution. We found no association between $PM_{2.5}$, CO or access to a cookstove and lung function. In keeping with findings from Peru, Nepal and Kenya, we observed poor correlation between CO and $PM_{2.5}$ measurements and different explanatory covariates for the two pollutants in our exposure models.[36] Although observed levels of exposure to both CO and $PM_{2.5}$ exceeded WHO upper safety limits, the duration of these high exposures was brief and we speculate that adverse pulmonary effects are limited by the low intensity of exposure in rural Malawi where most cooking is done outdoors. Similarly, we found that current smoking was not associated with FEV_1 in this population, likely reflecting the low intensity of tobacco use among smokers in this community; less than one-fifth of current or ex-smokers at baseline reported cigarette consumption of >10 pack years.

Strengths of our study include the collection of longitudinal lung function and personal air pollution exposure data in a rural cohort in one of the world's poorest countries; high-quality spirometry performed by BOLD-certified technicians, with external quality control of traces by an independent expert reviewer. Limitations include potential recall bias and highly variable responses to questionnaires, and bias introduced by those not attempting spirometry or lost to follow-up. Participants performing spirometry were younger and hence, it is likely that spirometric abnormalities, such as obstruction, which are associated with increasing age are likely to be under-represented. Throughout the study the team struggled with cultural beliefs that older members of the community were "too weak" or "physically unable" to attempt spirometry. One-third of participants from baseline were lost to follow-up by the end of the study; we were unable to ascertain the reasons for this due to limitations of the data collected, but comparison of the demographic data for those who remained in the study at each phase suggested that men and those with better education were more likely to be lost, reflecting the more economically active, mobile sector of society. We recognise that 3 years is a relatively short time period to track longitudinal changes in lung function but believe we would more likely observe any effect of the intervention during the CAPS study period when the use of the cookstoves was actively supported by a repair and maintenance programme. Given that the rate in decline in lung function we observed over 3 years was consistent with the rate of decline seen in healthy adults in Europe and North America, it seems likely that this observation is accurate and that a longer period of follow-up would not have yielded additional useful rate of decline information.

In conclusion, in our cohort of adults living in rural Malawi, we observed (a) reduced FVC compared with Caucasian reference populations, similar in relative magnitude to what we previously reported in children living in the same communities, (b) no evidence of accelerated decline in FEV_1 or FVC and c) no effect of access to cleaner-burning cookstoves on lung function decline. We suggest that future efforts to improve the lung health of those living in the poorest parts of the world should focus on antenatal and early childhood interventions to maximise lung growth and development. Further research is required to define the prognostic significance of reaching adulthood with suboptimal lung volumes, regardless of the comparative reference range in terms of morbidity, mortality and associated socioeconomic costs.

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