The societal burden of airflow obstruction and the potential impact of interventions amongst adults in Malawi.

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

by

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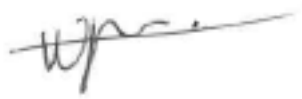
15th September 2022.

Declaration and affiliations

I, Martin W. Njoroge, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.



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Role of the candidate in the studies included in this thesis.

This thesis consists of four studies, two of which have already been published: chapter two[1] and chapter three[2]. For the 2019 follow-up study described in chapter two, as the local principal investigator (PI) I, developed and drafted the protocol and the data collection tools used in the study; put in and followed up on the research ethics committee applications both in-country and at the Liverpool School of Tropical Medicine; recruited, trained and managed the staff who collected the study data; oversaw all the data collection while in Chikwawa, Malawi and organized the participant recruitment schedules and compensation; and helped in the assessment of the quality of data collected especially spirometric data. For the health facility costing study described in chapter three I, developed the data collection tools and recruited and oversaw the staff who collected additional data at Queen Elizabeth Central Hospital in Blantyre, Malawi. For all the studies I, conducted all the data analysis included in this thesis, wrote the first version of the published manuscripts as thesis chapters and was the first and corresponding author of all the chapters that have been published in peer-reviewed journals.

Martin W. Njoroge: The societal burden of airflow obstruction and the potential impact of interventions amongst adults in Malawi.

Background

In Malawi previous studies report a high prevalence of abnormal lung function indicative of chronic respiratory disease (CRD) of which asthma and chronic obstructive pulmonary disease (COPD) are the most common. The natural history, health, and economic impact of abnormal lung function in Malawi is largely unknown.

Aims: 1) To estimate the health burden of airflow obstruction in Malawi; 2) To estimate current and future economic burden from a societal perspective of airflow obstruction in Malawi; 3) To estimate the cost-effectiveness of selected interventions for adults with airflow obstruction in Malawi.

Methods

We followed-up a cohort of 1481 adults recruited in 2014 and quantified their respiratory symptoms, health-related quality of life (HRQoL), and lung function spirometry. We conducted an economic study using patient health resource use and costs data obtained from three cohort studies in southern Malawi and health provider input and costs obtained from one of these studies and a bespoke costing study at a chest clinic. We evaluated the cost-effectiveness of the use of anticipatory 'emergency packs' of antibiotics and corticosteroids at home for COPD and inhaled beclomethasone and salbutamol for asthma using a Markov model.

Results

Forced expiratory volume in one second (FEV_1) declined by 53·4 ml/year (95% CI: 49.0, 57.8) and forced vital capacity (FVC) by 45.2 ml/year (95% CI: 39.2, 50.5). Chronic airflow obstruction increased from 9.5% (7.6%, 11.6%) in 2014 to 17.5% (15.3%, 19.9%) in 2019. Rate of FEV_1 decline was not associated with diagnosed chronic obstructive pulmonary disease (COPD), asthma, or spirometry consistent with asthma, COPD, or restriction. HRQoL was adversely associated with respiratory symptoms (dyspnoea, wheeze, cough), previous tuberculosis and declining FEV_1. These differences exceeded the minimally important difference.

Annual cost for an asthma patient is US$ 108.25 (95% CI: 86.68, 131.75) and for COPD US$ 143.39(95% CI: 123.61, 165.11), most of these costs being for hospital treatment of exacerbation. Guideline defined needs for 74.1% of those with asthma and 77.3% of those with COPD were unmet.

The COPD intervention dominated usual care in the people with mild COPD while the ICERs were US$ 72, US$ 102, and US$ 242 in people with mild asthma, moderate/severe asthma, and moderate/severe COPD respectively. The asthma intervention resulted in a life-years gain of 1.62 years in those with mild asthma and 1.29 years in those with moderate/severe asthma while the COPD intervention resulted in a life-years gain of 3.49 years in those mild COPD and 3.90 years in those moderate/severe COPD.

Implications

The high prevalence of COPD in Malawi adversely affects the quality of life and is, in part, a consequence of accelerated lung function decline. The evidence justifies the implementation of sustainable initiatives for widespread diagnosis and adoption of cost-effective CRD interventions such as antibiotics and corticosteroids at home for COPD and inhaled beclomethasone and salbutamol for asthma.

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To Ivy Kadzo '*Mame Mvera'*, for your love and support as we travelled across three countries in our PhD journeys. Thank you for patiently giving me an ear as I rambled and raved on regression, economic modelling, and R coding, some of which did not make sense to you. You encourage me to be better. *Uko sawa na wote malaika na mabawa yao*.

I am eternally grateful to my supervisors Graham Devereux, Louis Niessen, Angela Obasi and Jamie Rylance for their guidance and support throughout my PhD. Graham, you have been an incredible supervisor and mentor. Your wise counsel has been invaluable during my PhD study. Louis, you provided astute direction throughout my studies especially on the technical health economic components of my analysis. Angela and Jamie, you helped settle into my roles in Liverpool and Blantyre seamlessly. It has been an absolute pleasure working with all of you. You are the giants on whose shoulders I stand. I am extremely proud of the work that we have been able to do in this research project.

To the IMPALA directors and administrators specifically Martina, Debbie, and Elly, thank you for making my PhD journey smoother. I would like to thank Andrea Collins and Eve Worrall for their support as members of my Progress Assessment Panel.

The studies in chapter 2 and 4 would not have been possible without the study participants, community leaders and the study team in particular; Patrick Mjojo, Catherine Chirwa, Frank Jonas, Chifundo Mhango, Faith Zumazuma, Edgar Ngwira and Beatrice Chinoko.

To the many friends and colleagues at Malawi Liverpool Wellcome Trust Clinical Research programme (MLW), for providing a supportive environment and making my stay in Malawi memorable. I would especially like to thank the data team led by Clemens Masesa and the ethics team at MLW for their consistent assistance as I developed the ODK tools used to collect the study data and put in my ethics application.

To the Mategulas, thank you for being an amazing host when I first arrived in Malawi and helping me to settle in Blantyre. You made me feel at home.

To my parents Njoroge and Njeri, sister Muthoni and brother Mwangi thank you for being there for me always.

Mtaka cha mvunguni sharti ainame.

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Conducting ethical research Malawi Liverpool Wellcome Trust Clinical Research programme, Malawi.	May 2019 – May 2019
Introduction to Good Clinical Practice and Informed Consent & Introduction to screening and recruitment Malawi Liverpool Wellcome Trust Clinical Research programme, Malawi.	April 2019 – May 2019
Spirometry training Burden of Obstructive lung disease (BOLD) team, Imperial College London, United Kingdom.	June 2019 – June 2019
Decision Analytic Modelling for Economic Evaluation University of Glasgow, United Kingdom.	October 2018 – October 2018

Conferences.

- Poster presentation: *Health Economics of Lung Disease: The Adult Lung Diseases in Malawi Study.* Presented at: 23rd College of Medicine Research Dissemination Conference; 8th November 2019; Blantyre, Malawi.
- Oral presentation: *Assessing the societal burden of airflow obstruction and modelling the potential impact of leading interventions amongst adults in Malawi.* Presented at: 10th Kenya Medical Research Institute (KEMRI) Scientific and Health conference; 13th February 2020; Nairobi, Kenya.
- Oral presentation: *Changing lung function and associated health-related quality-of-life: a five-year cohort study of Malawian adults.* Presented at: Postgraduate research conference of the Liverpool School of Tropical Medicine (LSTM); 22nd June 2021; Liverpool, United Kingdom.

Awards.

June 2021	First prize at the Postgraduate research (PGR) student conference at the Liverpool School of Tropical Medicine.

Abbreviations

ACOS	Asthma COPD overlap syndrome
ATS	American Thoracic Society
BMI	Body mass index
BOLD	Burden of Obstructive Lung Disease
CAPS	Cooking and Pneumonia study
CEAC	Cost effectiveness acceptability curve
CHEERS	Consolidated health economic evaluation reporting standards
CI	Confidence interval
COMREC	College of Medicine Research and Ethics Committee
COPD	Chronic obstructive pulmonary disease
CRDs	Chronic respiratory diseases
DALYs	Disability-adjusted life years
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GDP	Gross domestic product
GLI	Global Lung Function Initiative
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HICs	High income countries
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroids
Int$	International dollars
IQR	Interquartile ranges
LABA	Long-acting beta-agonist
LLN	Lower limit of normal
LMICs	Low and middle-income countries
LABA	Long-acting beta-agonist
LSTM	Liverpool School of Tropical Medicine
MART	Maintenance and Reliver Therapy
MD	mean difference
MID	minimally important difference
ml	millilitre
MLE	Maximum likelihood estimation
MWK	Malawian Kwacha
NHANES	National Health and Nutrition Examination Survey
NCD	Non-communicable disease
NCDI	Non-communicable disease and injuries
NCRDs	Non-communicable respiratory diseases
OOP	Out-of-pocket
PI	Principal investigator
QALYs	Quality-adjusted life-years
QECH	Queen Elizabeth Central Hospital
SABA	Short-acting beta-agonists
SD	Standard deviation

SF–6D	Short-Form Six-Dimension
SF–12	12–item Short Form Survey
SSA	Sub-Saharan Africa
TB	Tuberculosis
µg	Microgram
UI	Uncertainty intervals
US$	United states dollar
VR–12	Veterans RAND 12 Item Health Survey
WHO	World Health Organisation
WTP	Willingness to pay

1 Introduction

1.1 Overview of non-communicable respiratory diseases

Globally, non-communicable respiratory diseases (NCRDs) are the third leading cause of non-communicable disease (NCD) death being responsible for 3.9 million deaths annually in 2017[3]. Amongst the NCRDs, asthma and chronic obstructive pulmonary disease (COPD) are the commonest with approximately 358 million affected by asthma, 174 million by COPD and the 3 million deaths annually from COPD, comprise an estimated 6% of all deaths worldwide[4,5].

Asthma is an NCRD characterised by reversible airflow obstruction. It is diagnosed through patient history, symptoms, and using tests such as spirometry, bronchodilator response and peak expiratory flow[6]. However, there is no single 'gold standard' test for asthma, the diagnosis remains essentially clinical. COPD is a chronic, slowly progressive disorder characterised by airflow obstruction that does not change markedly over several minutes or months. Most of the lung function impairment is fixed, although some reversibility can be produced by bronchodilator (or other) therapy[7]. It is the preferred name for the airflow obstruction associated the diseases of chronic bronchitis and emphysema[7]. It is diagnosed symptomatically and with spirometry tests. Conventionally a post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ≤ 0.7 confirms the presence of airflow limitation that is not fully reversible[8]. However, in recent years an obstructive spirometric 'abnormality' is being increasingly defined, particularly in research contexts, as a ratio of the forced expiratory volume in one second to the forced vital capacity (FEV_1/FVC) below the lower limit of normal (LLN) for the reference standard. Abnormal lung function can be characterised by an 'abnormal' spirometry test among other tests such as a plethysmography. Spirometry is 'abnormal' if it meets the restrictive or obstructive criteria as defined Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[9,10]. Restrictive

spirometric 'abnormality' is defined with FVC below the lower limit of normal, and an FEV_1 /FVC ratio $\geq$ LLN[9]. The lower limit of normal for FEV_1, FVC, and FEV_1/FVC ratio are frequently obtained from the NHANES III reference standard[11,12], the Global Lung Function Initiative (GLI) 2012 reference set[13], or from the local population if available. Although spirometry is commonly used to assess lung function, it is particularly useful in assessing COPD which is irreversible as compared to asthma which is considered reversible therefore under certain circumstances no airflow obstruction may be evident with asthma at the time of testing[14]. Because of the high prevalence of asthma and COPD, these conditions co-exist in a sizable proportion of individuals giving rise diagnostic uncertainty since they are both characterised by airflow obstruction, the term asthma COPD overlap syndrome (ACOS) is sometimes used as a diagnosis in these people.

It is becoming increasingly clear that most of the mortality and morbidity burden of NCRDs is in low and middle-income countries (LMICs)[3,15]. For instance, 90% of the deaths due to COPD globally occur in LMICs[16]. The environmental factors contributing to the high rates of airflow obstruction (asthma and COPD) in LMICs are not fully understood but are likely to include factors associated with urbanisation, early life/antenatal exposures[17] and exposure to indoor and outdoor pollution from biomass combustion and motor vehicles, respectively. The consequences of widespread airflow obstruction in LMICs are unknown but could have major public health implications because such airflow obstruction and limitation appear to start relatively young in life when people are economically active and looking after their families, moreover low FVC has been shown to be associated with premature mortality in high income countries (HICs)[18–20]. Despite the recent evidence of a high burden of airflow obstruction (including asthma, COPD) from general population community-based surveys representative of adults 18 years or older in Malawi and discussed further in chapter 2[21,22], there is a dearth

of data that describes the economic burden of these conditions. There is therefore a pressing need to better understand the economic costs of these diseases in LMICs given the high collective burden of airflow obstruction.

Many sub-Saharan Africa (SSA) countries face a double 'hit' of lung disease having a high risk of communicable disease such as Tuberculosis (TB) and at the same time a gradual increase of NCRDs such as COPD and asthma[23,24]. Notwithstanding, despite this increased burden of NCRDs, most patients do not have access to treatments for NCRDs[25] and those that do access treatments incur a substantial burden due to out-of-pocket payments and limited health insurance coverage in many households in LMICs[26]. This situation coupled with the financial burden of treating NCRDs could lead to pernicious outcomes for households including catastrophic health expenditures for many households in low-resource settings such as sub-Saharan Africa countries[27] due to their often-weak health systems and social care. It is therefore important that adequate planning and measures are put in place to ensure resilient social systems in these settings. This will entail a focus on reducing the risk factors associated with airflow obstruction and the planned deployment of affordable interventions in a timely manner such as inhaled therapies for asthma as recently recommended by a WHO report since they are cost-effective, and their use should be scaled up[28].

In SSA countries where resources are especially scarce, knowledge of the medium and long-term benefits and health costs of appropriate interventions to address the increasing NCRD burden are needed to best allocate limited health care resources. Decision-analytic modelling provides an evidence-based framework to estimate the lifetime health effects and costs of appropriate interventions and supports rational decision-making[29]. Several important studies have been conducted, mainly in high income countries, to model the disease progression of chronic respiratory disease specifically COPD[30]. For instance, a recent systematic review

documented 49 COPD models of which, 41 were Markov models, two were decision trees, one used a time-in-state model, two used an individual sampling modelling approach, one was a discrete-event simulation and two were system dynamics models[30]. These studies however are not easily transferable to LMIC settings due to differences in healthcare systems as most LMICs have low levels of health insurance coverage[31] leading to an increased use of out-of-pocket payments, lack of some modelled intervention and demographic differences and health risks profiles compared to HICs. In addition, there is a paucity of epidemiologic and economic studies that assess the impact of airway obstruction specifically asthma and COPD. It is therefore important that studies are conducted in LMIC settings that assess the economic impact of these diseases and related comorbidities in order to enable better planning and resource allocation. Capturing the costs of NCRDs given their long-term nature will require decision-analytic modelling in addition to empirical longitudinal studies so as to forecast their lifetime economic costs and quality of life utility measures. Malawi, a southeast African country provides an opportunity for this longitudinal observation with decision-analytic modelling approach given its high reported prevalence of 41.9% abnormal spirometry amongst adults[21]. Estimating the economic cost of obstructive conditions will provide a basis for intervention adoption and implementation within the health system and society. In addition, as part of this thesis develop decision-analytic modelling methodology was developed to provide a basis for designing interventions and intervention trials in Malawi and similar settings.

1.2 Motivation for the PhD

At conceptualization, the aim of this PhD study was to estimate the health burden and economic cost of airflow obstruction from a societal perspective and to identify efficient interventions to address this. Specifically, the research questions were:

1. What is the estimated health burden of airflow obstruction in Malawi?
2. What is the estimated current and future economic burden from a societal perspective, including households, of airflow obstruction in Malawi?
3. What is the estimated cost-effectiveness of selected key interventions for adults with airflow obstruction in Malawi?

This study also provided data to the Burden of Obstructive Lung Disease programme.

1.3 Structure of the thesis

The main results in this thesis are written in research paper format as some of them have already been published and the rest are intended for publication. Where a chapter has already been published, the final accepted version of the manuscript and the journal in which it was published are included in this thesis as appendices. Following this introductory chapter are five more chapters:

Chapter 2 provides a comprehensive description of the Chikwawa lung health cohort to date, the methods and procedures, tools used, a summary of the results from previously published analysis of the cohort and data that we collected in the community study that I led in 2019-2020. The study sampled adults representative of a rural Malawian population.

Chapter 3 estimates the annualised rate of change in lung function as measured by repeating spirometry and its associated risk factors in participants recruited into the Chikwawa lung health cohort. In addition, this chapter reports the change of prevalence of asthma and COPD, the most prevalent obstructive respiratory diseases, in a five-year follow-up period and the associated impact of the change in lung function on the health-related quality of life (HRQoL) of study participants.

Chapter 4 provides estimates for the annual per capita health resource use and cost of care to adults with asthma or COPD in Malawi. This chapter also reports the estimated prevalence

of unmet need for asthma or COPD care in Malawi both from people who are able to access health facility services and those who had no access to health facility services.

Chapter 5 provides the results from a Markov model I developed using empirical data from Malawi to evaluate the life-time economic cost and effects of possible interventions for asthma and COPD for adults in the Malawian society. This model can be adapted to provide useful intervention cost-effective results to countries with similar health systems to the Malawian health system.

Chapter 6 is a concluding discussion chapter summarising all the findings from the four studies conducted in this PhD while making relevant policy recommendations and looks to the future on the implications on future works.

1.4 Additional information

1.4.1 Ethics statements

The study protocol was approved by the Imperial College Research Ethics Committee (17IC4272), Liverpool School of Tropical Medicine Research Ethics Committee (19-005) and the Malawi College of Medicine Research and Ethics Committee (P.03/19/2617). Written informed consent was obtained from all the participants in this study for the follow-up and for the second interview and examination. All the approval letters can be found in appendix section A: Ethical approvals.

1.4.2 Challenges faced in this PhD project.

This PhD project faced various challenges in the course of being executed. Among them were; Cyclone Idai in March 2019, a category 3 tropical cyclone in Southern Africa, disrupted my data collection in Malawi; and the COVID – 19 pandemic affected not only my PhD project but the entire world in a profound way. Nevertheless, we finished all the fieldwork activities required for this research project, analysed, and published two manuscripts presented in

chapter two and three. Chapter three and four will be submitted for publication in the immediate future.

In addition to these acts of God hurdles above, conducting spirometry in the field, in a resource constrained setting with limited locally available spirometry reference sets from either NHANES III[11,12], or the GLI 2012[13] reference standards coupled with my prevision training as a statistician and not a pulmonologist was a challenge. I undertook a spirometry training led by the Burden of Obstructive lung disease (BOLD) team in 2019 prior to data collection with the aim of improving my knowledge and skill in collecting high quality spirometry data. Alongside that, I used the GLI 2012[13] reference standards in my analysis as it contains data from similar African populations to Malawi whilst the NHANES III reference set[11,12] is based on United States populations.

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2 Cohort profile: The Chikwawa lung health cohort; a population-based observational non-communicable respiratory disease study of adults in Malawi

2.1 Overview

This chapter provides a detailed description of all the methods and procedures that were used to set up and conduct a follow-up study in Chikwawa. It documents the processes that were involved and the data that were collected in the baseline study and the 2015 – 2017 follow-up of the Chikwawa lung health cohort and reports a summary of the findings from these studies which provide the rationale for my study. The next chapter of my thesis, chapter 3, builds on the previous studies conducted within the Chikwawa lung health cohort by conducting a further follow-up study in 2019 – 2021 and reporting the findings with the aim of addressing the first objective of my thesis of estimating the health burden of airflow obstruction in Malawi. The chapter was published as Njoroge MW, Rylance S, Nightingale R, Gordon S, Mortimer K, Burney P, et al. **Cohort profile: The Chikwawa lung health cohort; a population-based observational non-communicable respiratory disease study of adults in Malawi.** PLoS One 2020; 15:e0242226.

2.2 Role of the candidate

I developed the data collection tools, drafted the study protocol, the first version of the manuscript and was the in-country principal investigator (PI) of the latest phase of the Chikwawa lung health cohort conducted in the year 2019 to 2021. In my role as the local PI, I applied for both in-county and LSTM ethics approval, recruited and trained the fieldworker staff, planned the schedules for study participant recruitment and managed all the fieldworker activities. Revisions were made with feedback, input, and guidance from my supervisors Graham Devereux, Louis W. Niessen, Angela Obasi and Jamie Rylance. Kevin Mortimer, Rebecca Nightingale and Sarah Rylance set up the baseline study that led to the

formation of the Chikwawa lung health cohort. Stephen Gordon and Peter Burney provided comments in several rounds of review of the manuscript.

2.3 Abstract

2.3.1 Purpose

The aim of this section is to provide a detailed description of the Chikwawa lung health cohort that was established in rural Malawi to prospectively determine the prevalence and causes of lung disease amongst the general population of adults living in a low-income rural setting in Sub-Saharan Africa.

2.3.2 Participants

A total of 1481 participants were randomly identified and recruited in 2014 for the baseline study. Data were collected on demographic, socio-economic status, respiratory symptoms, and potentially relevant exposures such as smoking, household fuels, environmental exposures, occupational history/exposures, dietary intake, healthcare utilization, cost (medication, outpatient visits and inpatient admissions) and productivity losses. Spirometry was performed to assess lung function. At baseline, 56.9% of the participants were female, mean age was 43.8 (SD:17.8) and mean body mass index (BMI) was 21.6 Kg/m^2 (SD: 3.46).

2.3.3 Findings to date

The cohort has reported the prevalence of chronic respiratory symptoms (13.6%, 95% confidence interval [CI], 11.9 – 15.4), spirometric obstruction (8.7%, 95% CI, 7.0 – 10.7), and spirometric restriction (34.8%, 95% CI, 31.7 – 38.0). Additionally, an annual decline in forced expiratory volume in one second [FEV_1] of 30.9mL/year (95% CI: 21.6 to 40.1) and forced vital capacity [FVC] by 38.3 mL/year (95% CI: 28.5 to 48.1) has been reported.

2.3.4 Future plans

The ongoing phases of follow-up will determine the annual rate of decline in lung function as measured through spirometry and the development of airflow obstruction and restriction, and relate these to morbidity, mortality and economic cost of airflow obstruction and

restriction. Population-based mathematical models will be developed driven by the empirical data from the cohort and national population data for Malawi to assess the effects of interventions and programmes to address the lung burden in Malawi. The present follow-up study started in 2019.

Keywords: Cohort studies**,** Non-communicable respiratory disease, Asthma, Chronic obstructive pulmonary disease, economic modelling

2.4 Introduction

Globally, non-communicable respiratory diseases (NCRD) are the third leading cause of non-communicable disease (NCD) mortality, causing an estimated 4 million deaths each year[1]. Amongst the NCRD, asthma and chronic obstructive pulmonary disease (COPD) are the most prevalent, affecting approximately 358 million and 174 million people respectively[2]. Annually, COPD causes 3 million deaths accounting for 6% of all deaths worldwide[2–4]. Furthermore, the deaths from these diseases are rising globally[5] in part due to increased longevity and changes in population structure[6].

The majority of the burden of NCRD mortality and morbidity is in low and middle-income countries (LMIC)[1,7], which now account for 90% of COPD deaths[8]. Several community based studies in LMIC have documented a high prevalence of abnormal lung function, both obstructive and restrictive (low lung volumes)[9–15], whilst several have documented low prevalence of COPD[16,17] but high prevalence of respiratory symptoms[17]. In contrast, very few observational cohort studies have reported and described the health and economic burden of NCRD[18,19], especially in LMIC settings. Their prevalence means that there is a pressing need to better document the life course epidemiology and the related health and economic burden of abnormal (obstructive and restrictive) lung function in LMIC[10,11].

Malawi remains one of the poorest countries in the world[20] with 83% of its 18 million inhabitants living in rural areas[21]. With a gross domestic product (GDP) per capita of $300, over half the households live below the poverty line (using the international poverty line of US$ 1.90 per person per day)[22], and about 50% of the national health expenditure is funded from external donors[23,24]. In common with sub-Saharan African (SSA) countries, Malawi is at the intersection of high rates of communicable respiratory diseases (Tuberculosis (TB), pneumonia), and increasing NCRD[25–27]. Although Malawi has a well-established TB control

programme, only 10 – 20% of patients presenting at primary healthcare facilities with a persistent cough have TB[28]. The prevalence of diagnosed NCRD such as COPD, asthma and pulmonary fibrosis is essentially unknown[29] because lung function testing is not available out with research settings[30]. In Chikwawa where this study is based, lung function testing is not available at primary health facilities or secondary care (Chikwawa District Hospital). There is very limited capacity to perform spirometry in tertiary care, and this is provided by research staff, and for most patients, transport cost would prevent them from travelling to access this. Recently, however, studies have reported substantial levels of abnormal lung function in Malawi, with spirometric evidence of restrictive and obstructive deficits present in 34.8% (95% CI: 31.7%, 38.0%) and 8.7% (7.0%, 10.7%) of rural adults and 38.6% (34.4%, 42.8%) and 4.2% (2.0%, 6.4%) of urban adults respectively[10]. Spirometric deficits were defined according to the NHANES III Caucasian references[31]. What is not known is, whether, and how these spirometric deficits impact on the everyday lives of the country's people and health system. Potentially, as in other low-income situations, the economic burden of NCRD may have serious adverse outcomes for households including unpredictable household expenditures due to complications and catastrophic health expenditure[32].

To examine the health and economic burden of NCRD, including abnormal lung function in Malawi, our prospective study aims to follow up a population-based cohort of participants in the rural district of Chikwawa, in southern Malawi, who were recruited to a longitudinal follow-up spirometry study conducted between August 2014 and July 2015 (the Chikwawa lung health cohort)[11,15]. The primary objectives of the current study are to; (i) estimate the annualised rate of change in lung function by age and sex as determined by repeating spirometry; (ii) to develop a mathematical population model based on the cohort findings that estimates the life-time health impact of airflow obstruction in Malawian adults in

disability-adjusted life years (DALYS) or quality-adjusted life years (QALYs); (iii) estimate the health resource use and lifetime costs in the cohort of Malawian adults with airflow obstruction in international dollars (Int$); (iv) produce model estimates of the lifetime cost effectiveness (Int$/DALY) or (Int$/QALY) of selected key intervention compared with current practice to define optimum packages of interventions; and (v), recreate these analyses for Malawian adults with low lung volumes. The economic cost will be from a societal perspective and will include health sector costs, patient/family and carer costs and productivity losses[33]. Presently, the Malawian health system recommends the use of salbutamol and beclomethasone inhalers and prednisolone as interventions for chronic asthma management and salbutamol inhalers, prednisolone and hydrocortisone injections as interventions for acute asthma[34] but these interventions are only available in 8% of urban health facilities and 2% of rural health facilities in Malawi[35]. The current study will determine whether the substantial levels of abnormal lung function in Malawian adults are clinically and societally important not only currently, but also in the future by estimating the economic cost of obstructive and restrictive conditions. In addition, the present study will provide a basis for NCRD intervention adoption and implementation within the Malawian health system, society and similar settings.

The aim of this cohort profile paper is to provide a comprehensive description of the Chikwawa lung health cohort as a research resource for potential collaborations, including an overview of the collected data, a description of the baseline characteristics and a summary of the main results published so far.

2.5 Cohort description and methods

2.5.1 Setting

The study is currently conducted in Chikwawa district, located in Southern region of Malawi. (See Figure 2-1). Figure 2-2 are images illustrative of a typical Chikwawa village.

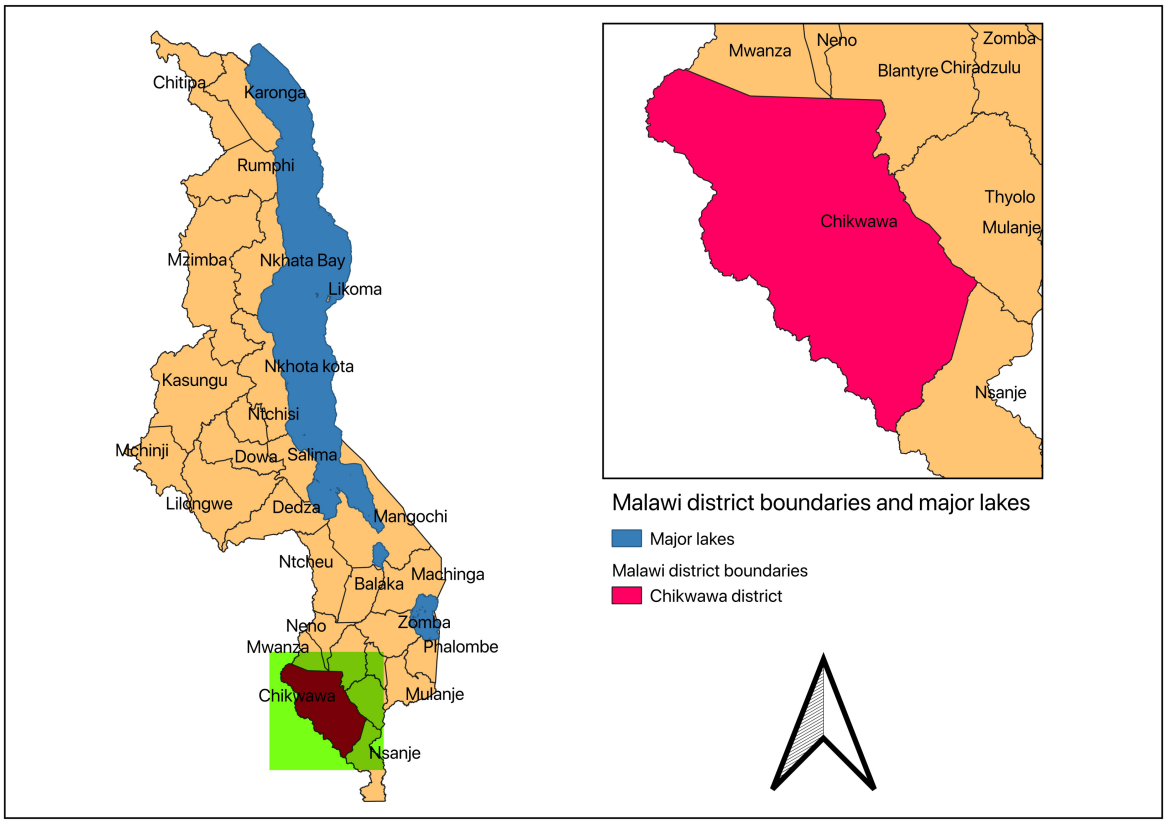

Figure 2-1: Districts in Malawi. Inset map highlights Chikwawa district, the study area. (Created using the open source QGIS ver. 3.8. Zanzibar (QGIS Development Team, 2020, https://qgis.org)).




Figure 2-2: Photos illustrate of a typical Chikwawa village.

2.5.2 Study population

The Chikwawa lung health cohort was initiated alongside the Cooking and Pneumonia study (CAPS)[11,36] (Trial registered with ISRCTN, number ISRCTN59448623). CAPS was a cluster randomized trial that investigated the health effects of a cleaner-biomass fuel cookstove intervention[36]. The aim of setting up the Chikwawa lung health cohort was to determine the prevalence and determinates of lung disease amongst adults in Chikwawa, rural Malawi[11]. Since inception, two rounds of follow-up studies have been conducted with the Chikwawa lung health cohort aiming to assess the determinants of lung function trajectories as affected by personal air pollutant exposures, including the CAPS cookstove intervention[15]. The current study will provide additional longitudinal data by further following up participants from the Chikwawa lung health cohort who still reside in Chikwawa and who were recruited to the baseline study in 2014 – 2015[11] and quantify associated risk factors, health utilisation use and economic burden.

2.5.3 Statistical analyses

The sociodemographic and clinical variables were determined for the sample using frequencies and proportions for categorical variables and means and standard deviation for continuous variables. Chi-square and t test were used to investigate associations between gender and the other variables

2.5.4 Baseline participant recruitment

The participants were originally recruited in 2014 – 2015. The participants were selected through random sampling of a list of adults living in each of the 50 villages participating in CAPS[11]. The participants included those who took part in the CAPS intervention and those who did not but resided in villages where the CAPS intervention was being implemented. The list of adults was obtained from local community liaison personnel from each village following

a series of community engagement events with the village leaders such as chiefs and other community representatives[11]. The random selection was conducted by an independent statistician at the Burden of Obstructive Lung Disease (BOLD) centre in London in accordance with the BOLD protocol[37]. The identified individuals comprised a population-representative, age and gender stratified, sample of adults who were then invited to participate in the 2014 – 2015 baseline study. Participants had to provide written informed consent or an independently witnessed thumbprint to be included in the study[11]. Those who were acutely unwell or pregnant women or were non-permanent residents of Chikwawa were excluded from the baseline study[11].

A total of 3000 adults were invited to participate in the baseline study of which 1481 (49.3%) agreed to participate[11]. Participants were stratified into two age groups: 18 – 39 years and 40 years and above. In order to provide an estimate of chronic airflow limitation prevalence in the stratum with a precision (95% CI) of +3.3% to 5.0% and assuming a prevalence of 10% to 25%, a total sample of 1200 participants was estimated allowing for unequal age and gender distribution, refusals and inability to provide spirometry measurements of acceptable quality[11]. Table 2-1 Table 2-1 Demographic characteristics of cohort participants.below summarises the age and sex characteristics of those who agreed to participate in the study compared to those who did not.

Table 2-1 Demographic characteristics of cohort participants.

		Consenting participants n = 1481	**Selected, did not give consent n = 1519**
Age, mean (SD)		43.9 (17.8)	40.3 (16.5)
Age categories years n (%)	<39	685 (46.3%)	765 (50.3%)
	40 – 49	258 (17.4%)	336 (22.1%)
	50 – 59	217 (14.7%)	179 (11.8%)
	60 – 69	161 (10.9%)	150 (9.9%)
	>70	160 (10.8%)	89 (5.9%)

Sex	Female	844 (57.0%)	757 (49.9%)
	Male	637 (43.0%)	762 (50.2%)

2.5.5 Participant tracking and recruitment procedures for the current longitudinal study.

In the current study, the adult participants have been tracked from participant logs developed in the original baseline study[11]. The participant log contains the person's name, study identification number, age, gender, and village of residence. Community liaison personnel and chiefs were asked to help identify the household of each study participant to maximise fidelity. Study staff then approached the participant in their households, obtained informed consent, geolocation, and agreed a suitable time to collect the lung function, environmental exposures, and socioeconomic data.

2.5.6 How often has the cohort been followed up?

Study participants have been followed up twice prior to the current study. The baseline study was conducted between August 2014 – July 2015[11] with an aim of determining the prevalence and determinates of lung disease. The first and second follow-up studies were between August 2015 – November 2017[15] aiming to assess the determinants of lung function trajectories as affected by personal air pollutant exposures, including the CAPS cookstove intervention. The current round of follow-up took place between July 2019 – March 2021 (see Figure 2-3).

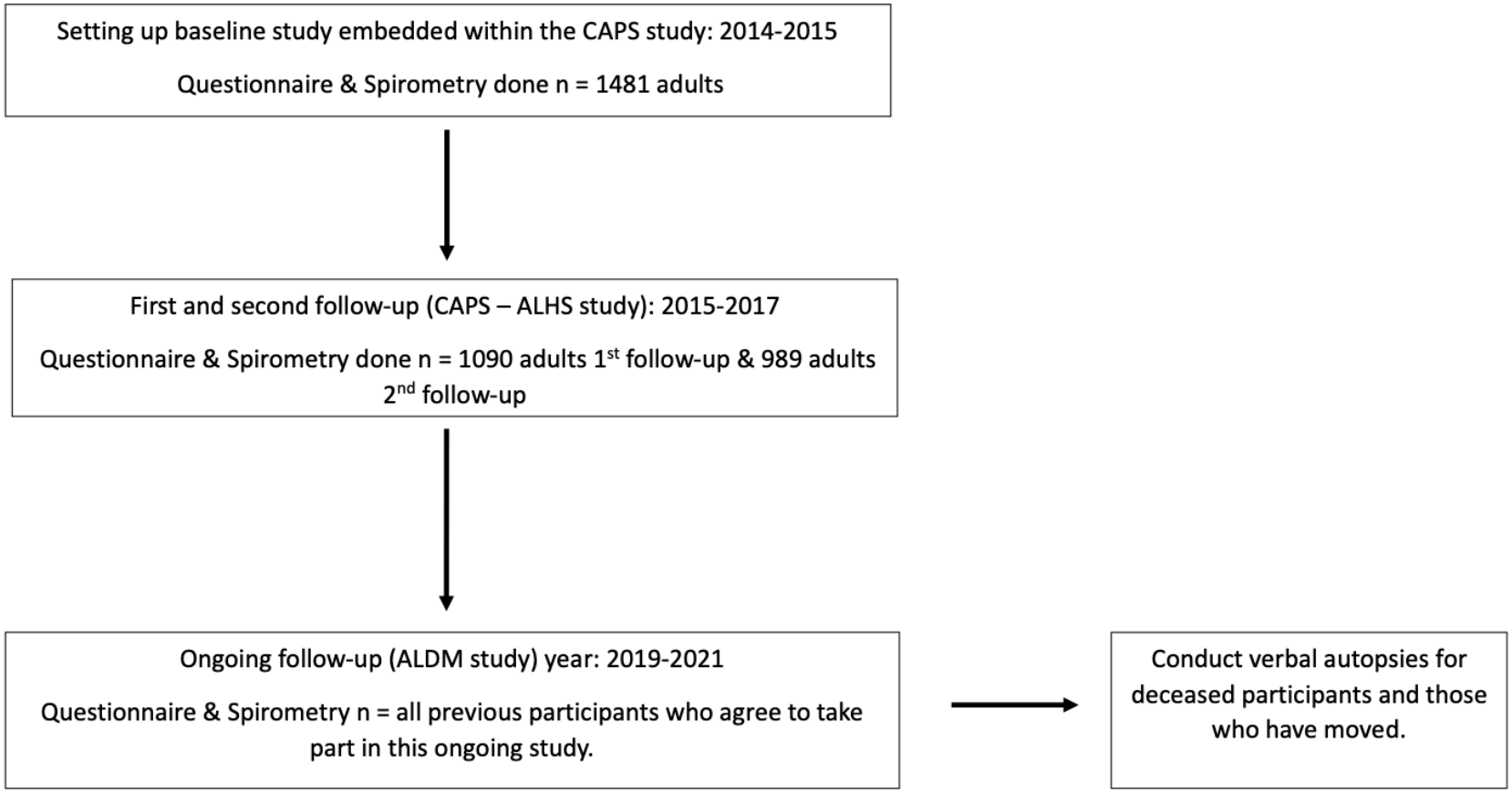

Figure 2-3: Flow chart of participant recruitment and follow-up schedule.

2.5.7 Assessment of exposures

In the baseline study, structured interviews were used to collect data on demographic, socio-economic status, respiratory symptoms, and potentially relevant exposures such as smoking[38,39], household fuels[38,40], environmental exposures[39,41], and occupational history[39,42]. In addition to the data collected for the baseline study in the current 2019-2021 follow up, we are collecting additional data on dietary intakes[39,43], healthcare utilization, cost (medication, outpatient visits and inpatient admissions) and productivity losses. All the questionnaires we used are presented in the appendix (see appendix B: Data collection tools in English and Chichewa)

The following anthropometric measures have been recorded at each phase of follow up: height, weight, hip, waist, and neck circumferences, ulna, and fibula lengths. Lung function (forced expiratory volume in one second [FEV_1] and forced vital capacity [FVC]) are measured using the ndd EasyOne Spirometer (ndd Medizintechnik AG, Zurich, Switzerland), before and 15 minutes after administration of inhaled salbutamol (200 µg) administered via spacer device. The contraindications for spirometry include: in the previous three months; thoracic or abdominal surgery, acute coronary syndrome, detached retina or eye surgery; hospitalisation for any other cardiovascular reason in the previous month; final trimester of pregnancy; a resting heart rate > 120 beats per minute and current treatment for tuberculosis[44].

Spirometry has been conducted by trained and certified technicians who received regular feedback on spirogram quality in accordance with the BOLD protocol[37]. The quality of each spirogram has been reviewed and scored based on the American Thoracic Society (ATS) and European Respiratory Society (ERS) acceptability and reproducibility criteria[45].

In the current phase of follow-up, verbal autopsies were conducted for the 2014 – 2015 baseline participants who have died, and a questionnaire was administered to the next of kin for those who were unobtainable due to being no longer resident in Chikwawa. The data and variables collected in the Chikwawa lung health cohort are described in Table 2-2.

Table 2-2: Summary of measurements in the Chikwawa lung health cohort.

Phase	Spirometry measured	Anthropometric measured	Questionnaires & tools administered
Baseline 2014 – 2015[11]	• Forced vital capacity (FVC) • Forced expiratory volume in 1 second (FEV_1) • Forced expiratory volume in 6 seconds (FEV_6)	• Weight • Height • Waist & hip circumference	• Socio-economic status • Demographic characteristics • Environmental exposures • Smoking history • History of respiratory disease (Tuberculosis, Asthma and COPD).
First and second follow-up (this follow-up phase was called the CAPS-Adult Lung Health study) 2015 – 2017[15]	• FVC • FEV_1 • $FEV_{6.}$	• Weight • Height • Waist & hip circumference	• Socio-economic status • Demographic characteristics • Environmental exposures • Smoking history • History of respiratory disease (Tuberculosis, Asthma and COPD). • Personal air pollutant monitoring
Ongoing (this follow-up phase is called Adult Lung Diseases in Malawi study) 2019 – 2021	• FVC • FEV_1 • $FEV_{6.}$	• Weight, • Height; • Ulna & fibula lengths; • Neck, waist & hip circumference.	• Socio-economic status • Demographic characteristics • Environmental exposures • Smoking history • History of respiratory disease (Tuberculosis, Asthma and COPD) • History of health utilization and costs (medication, outpatient & inpatient) • Productivity losses • Household dietary consumption

2.5.8 Ethical approval

The study protocol was approved by the Imperial College Research Ethics Committee (17IC4272), Liverpool School of Tropical Medicine Research Ethics Committee (19-005) and the Malawi College of Medicine Research and Ethics Committee (COMREC, P.03/19/2617). Written informed consent was obtained from all the participants in this study for the follow-up and for the second interview and examination.

2.5.9 Participant and public involvement

Participants were not involved in in setting research questions or the outcome measures but have been instrumental in implementation of the study. Participants and the public were involved in the dissemination of baseline information nationally through the Ministry of Health, and in the Chikwawa community from which the data were collected through the Chikwawa Health Research Committee and the Chiefs and community leaders from the villages from where we collected our data. These activities have encouraged community buy-in and involvement in the subsequent rounds of follow-up within the cohort.

2.6 Findings to date and discussion

The Chikwawa lung health cohort has provided data characterising the burden of chronic respiratory symptoms, abnormal spirometry and air pollution exposures and risk factors from an adult population in Malawi[11,36]. These data have contributed to the understanding of NCRD in LMIC. The baseline characteristics of the Chikwawa lung health cohort when established in 2014 – 2015 are outlined in Table 2-3. At baseline, a total of 1481 participants were recruited of which 637 (43.0%) were male and 844 (57.0%) were female[11]. The mean age was 43.9 years (SD: 17.8), mean body mass index (BMI) was 21.6 Kg/m^2 (SD: 3.46). Cigarette smoking rates were 22.1% (n=327) were current or ever smokers of which the majority were men (n = 255, 78.0%). There was no difference in ages between the men and women (see Table 2-3).

Table 2-3: Baseline demographic, anthropometric and symptomatic characterises of the Chikwawa lung health cohort collected 2014 – 2015.

Variable (n)		**n (%) (total = 1481)**	**Male n (%) (total = 637)**	**Female n (%) (total = 844)**	**P value (X^2)$^{\Psi}$**
Age group (years)	<39	685 (46.3%)	288 (45.2%)	397 (47.0%)	0.150
	40 – 49	258 (17.4%)	103 (16.2%)	162 (18.4%)	
	50 – 59	217 (14.7%)	110 (17.3%)	110 (12.7%)	
	60 – 69	161 (10.9%)	70 (11.0%)	96 (10.8%)	
	>70	160 (10.8%)	66 (10.4%)	99 (11.1%)	
BMI [##]	Underweight (< 18.5)	182 (13.9%)	84 (13.2%)	98 (11.6%)	<0.001
	Normal weight (≥18.5; <25.0)	950 (72.8%)	465 (73.0%)	485 (57.5%)	
	Overweight (≥25.0; <30.0)	133 (10.2%)	36 (5.7%)	97 (11.5%)	
	Obese (≥ 30.0)	40 (3.1%)	2 (0.3%)	38 (4.5%)	
Smoking	Never	1154 (77.9%)	382 (60.0%)	772 (91.5%)	<0.001
	Current	205 (13.8%)	165 (25.9%)	40 (4.7%)	
	Former	122 (8.2%)	90 (14.1%)	32 (3.8%)	
Symptoms					
Cough on most days of the month for at least three months of the year.		167 (11.3%)	81 (12.7%)	86 (10.2%)	0.148
Usually brings up phlegm from chest		39 (2.6%)	21 (3.3%)	18 (2.1%)	0.221
Wheezing/whistling in chest in the past 12 months in the absence of a cold.		24 (1.6%)	15 (2.4%)	9 (1.1%)	0.082
MRC dyspnoea score II[46,47]:shortness of breath when hurrying on the level or walking up a slight hill.		23 (1.6%)	11 (1.7%)	12 (1.4%)	0.766
Any respiratory symptoms		203 (13.7%)	105 (16.5%)	98 (11.6%)	0.008
Functional limitation: breathing problems interfere with usual daily activities.		44 (3.0%)	21 (3.3%)	23 (2.7%)	0.624
Diagnosed lung disease					
Asthma		51 (3.4%)	23(3.6%)	28 (3.3%)	0.868
Asthma, emphysema, chronic bronchitis, or COPD		59 (4.0%)	28 (4.4%)	31 (3.7%)	0.566
Previous TB		47 (3.2%)	16 (2.5%)	31 (3.7%)	0.268

n= 1341**.** BMI classification based on WHO guidelines[48].

Ψ Comparison of proportions using Pearson's chi square test.

2.6.1 The frequency of chronic respiratory symptoms and abnormal spirometry.

Among the participants at recruitment in 2014-15, with interpretable and reliable spirometry (n = 886)[37], spirometric obstruction (defined as $FEV_1/FVC < 0.70$) and spirometric restriction (defined as $FEV_1/FVC > 0.70$ and post-bronchodilator FVC < 80% predicted)[31] were present in 8.7% (95% CI: 7.0%, 10.7%) and 34.8% (95% CI: 31.7%, 38.0%) of the participants respectively according to the NHANES III Caucasian references[11]. 13.7% reported either having a 'cough without having a cold', 'bringing up phlegm from your chest', 'wheezing in your chest', 'shortness of breath when hurrying on the level or walking up a slight hill', or 'breathing problems interfering with your daily activity' while 11.3% reported a 'cough on most days of the month for at least three months per year'. 3.4% were diagnosed with asthma while 4.0% were diagnosed with either asthma, emphysema, chronic bronchitis, or COPD (see Table 2-3). The 2017 follow-up found that, when compared to the NHANES III African American reference ranges, spirometric obstruction and restriction were present in 11.5% (95% CI: 9.6%, 13.5%) and 7.7% (95% CI: 6.2%, 9.5%) of the participants respectively[15]. For participants who had been followed up in both 2015 to 2017, an overall annual rate of lung function decline in forced expiratory volume in one second [FEV_1] of 30.9mL/year (95% CI: 21.6 to 40.1) and forced vital capacity [FVC] by 38.3 mL/year (95% CI: 28.5 to 48.1) has been reported[15]. Presently, we are able to trace over 85% of the participants in the Chikwawa lung health cohort and have invited them to participate in this current phase of follow-up. The ongoing analysis of the data at a later time point for follow up will provide better estimates for annual rate of lung function decline.

2.6.2 Present research plans.

The ongoing current phase of follow-up of the Chikwawa lung health cohort will determine the annual rate of decline in lung function as measured through spirometry, morbidity,

mortality and economic cost of airflow obstruction and restriction and develop population-based mathematical models driven by the empirical data from the cohort and national population data for Malawi to assess the effects of interventions and programmes to address the lung burden in Malawi. It is expected that this further phase of follow-up will add to the body of knowledge of the life course of NCRD in LMIC and further refine and add to the validity of the health economic models developed. This phase of follow-up will also provide data to the BOLD initiative[37].

2.6.3 Strengths and limitations

The Chikwawa lung health cohort appears to be the only one of its kind in a low-income country setting aiming to investigate the economic costs over the life course of non-communicable respiratory disease. This cohort represents an opportunity to develop and model cost-effective interventions and programmes for this setting. The baseline cohort was conducted alongside a rigorously conducted cluster randomised control trial. Despite local complexities, we presently have identified over 85% of the baseline cohort to be included in the current phase of follow-up.

Systematic bias may be introduced through the self-selection of the participants who agreed to take part in the study to date and the migration of individuals from Chikwawa. Although we have been able to track over 85% of the original Chikwawa lung health cohort and have invited them to participate in the current phase of follow-up, the participants who can be traced and from whom data are collected may differ from those who cannot be traced or do not attend follow-up. Similarly, at baseline, the participants who agreed to be consented were slightly older and mainly women. The process of verbal autopsies for those who have died[49], and collection of data from the next of kin of those who have moved away, may shed some light on the status of those who have moved away from Chikwawa and deaths from

respiratory causes will be of particular interest in the current follow-up. The other limitation identified in this study is recall bias. This is due to most of the data being collected through administering questionnaires in a structured interview format, one can expect recall bias over the follow-up period. We are using tested and validated tools in addition to well-trained experienced interviewers to minimize this bias.

The main strength of the cohort is the collection of initial objective measures of lung function using spirometry conducted to internationally agreed standards[37,45] and on two further occasions over a 3-year period. This will provide valuable insights into the health relevance and natural history of abnormal lung functions in an LMIC setting. Previous studies in the United States, the United Kingdom and Australia have reported the annual rate of decline of FEV_1 in adults to be 18 ml/year standard deviation (SD) = 2.5[50], 33ml/year (SD = 1.5)[51] and 45ml/year (SD = 83)[52].

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3 Changing lung function and associated health-related quality-of-life: a five-year cohort study of Malawian adults.

3.1 Overview

This chapter provides the results from an analysis of the estimation of the rate of change in lung function as measured by repeating spirometry and its associated risk factors in participants recruited into the Chikwawa lung health cohort. This chapter also reports the change in prevalence of asthma and COPD and associated impact on the health-related quality of life of the participants due to the natural history of abnormal lung function. The findings from this chapter address the first and second objectives of my thesis of estimating the current and future health and economic burden of airflow obstruction in Malawi. The chapter was published as Njoroge MW, Mjojo P, Chirwa C, Rylance S, et al. **Changing lung function and associated health-related quality-of-life: A five-year cohort study of Malawian adults.** EClinicalMedicine 2021; 41: 101166.

3.2 Role of the candidate

I conducted all the data analysis in this chapter, wrote the first version of the manuscript as a thesis chapter, was the first author and corresponding author of the resultant published manuscript and the in-country principal investigator (PI) of this study. Revisions were made with feedback, input, and guidance from my supervisors Graham Devereux, Louis W. Niessen, Angela Obasi and Jamie Rylance. All the other co-authors provided comments in several rounds of review of the manuscript.

3.3 Abstract

3.3.1 Background

In sub-Saharan Africa cross-sectional studies report a high prevalence of abnormal lung function indicative of chronic respiratory disease. The natural history and health impact of this abnormal lung function in LMICs is largely unknown.

3.3.2 Methods

A cohort of 1481 adults representative of rural Chikwawa in Malawi were recruited in 2014 and followed-up in 2019. Respiratory symptoms and health-related quality of life (HRQoL) were quantified. Lung function was measured by spirometry.

3.3.3 Findings

1282 (83%) adults participated; spirometry was available for 1082 (73%). Mean (SD) age 49·5 (17·0) years, 278 (23%) had ever smoked, and 724 (59%) were women. Forced expiratory volume in one second (FEV_1) declined by 53·4 ml/year (95% CI: 49·0, 57·8) and forced vital capacity (FVC) by 45·2 ml/year (95% CI: 39·2, 50·5). Chronic airflow obstruction increased from 9·5% (7·6%, 11·6%) in 2014 to 17·5% (15·3%, 19·9%) in 2019. There was no change in diagnosed asthma or in spirometry consistent with asthma or restriction. Rate of FEV_1 decline was not associated with diagnosed chronic obstructive pulmonary disease (COPD), asthma, or spirometry consistent with asthma, COPD, or restriction. HRQoL was adversely associated with respiratory symptoms (dyspnoea, wheeze, cough), previous tuberculosis, declining FEV_1 and spirometry consistent with asthma or restriction. These differences exceeded the minimally important difference.

3.3.4 Interpretation

In this cohort, the increasing prevalence of COPD is associated with the high rate of FEV_1 decline and lung function deficits present before recruitment. Respiratory symptoms and sub-optimal lung function are independently associated with reduced HRQoL.

3.4 Research in context

3.4.1 Evidence before this study

Multi-national studies report a high prevalence of abnormal lung function in low- and middle-income countries (LMICs) indicative if airflow obstruction (COPD, asthma) and restriction. Very few studies have conducted longitudinal measurement to investigate the natural history of lung function in LMICs and impact on health-related quality of life (HRQoL).

3.4.2 Added value of this study

This study in rural Malawi showed that in a general population of adults, the prevalence of COPD nearly doubled from 9·5% to 17·5% in 5 years. The rate of lung function decline in predominantly non-smoking adults is comparable with that reported for smokers of $\geq$ 15 cigarettes a day in high income countries. The respiratory symptoms and reductions in lung function experienced by adult Malawians are associated with clinically significant reductions in HRQoL.

3.4.3 Implications of all the available evidence

The high prevalence of COPD in sub-Saharan Africa adversely affects the quality of life and is, in part, a consequence of accelerated lung function decline. The evidence justifies the implementation of sustainable initiatives for widespread diagnosis and management of chronic respiratory diseases in sub-Saharan Africa.

3.5 Introduction

Chronic obstructive pulmonary disease (COPD) and asthma are the most prevalent chronic respiratory diseases (CRDs)[1]. Globally, COPD accounts for three million deaths annually, 90% of which are in low- and middle-income countries (LMICs)[1,2]. Asthma is the most common CRD, affecting 358 million people, it is the commonest chronic disease of childhood and remains a burden to individuals, their families, and healthcare systems[1]. In LMICs, population-based surveys have reported a high prevalence of respiratory symptoms[3–5], obstructive and restrictive lung function[6,7], but low prevalence of diagnosed COPD[8] suggesting an unrecognised clinical need. International guideline recommendations are that asthma and COPD require long term treatment and follow-up[9,10]. Knowing the true lifetime CRD burden may potentially have profound implications for provision of respiratory health services. However, given the scarcity of resources competing for healthcare priority there is a pressing need to better document the impact of CRD's on long-term general morbidity. Few studies have reported and described the general health impact of diagnosed (and undiagnosed) asthma and COPD in LMICs[11].

In Malawi, two studies have reported significant levels of abnormal lung function with restrictive and obstructive lung function deficits being present in 34·8% (95% CI: 31·7%, 38·0%) and 8·7% (7·0%, 10·7%) of rural adults, respectively, and 38·6% (34·4%, 42·8%) and 4·2% (2·0%, 6·4%) of urban adults, respectively[5,12]. Whether these lung function deficits arise from failure to attain the normal lung function plateau in the third decade and/or from subsequent accelerated decline of lung function remains to be ascertained. In addition, the impact of these lung function deficits on general health status, peoples' everyday lives, and subsequent health service needs, is largely unknown in this and other LMICs settings.

We report here the findings of a cohort study in rural Malawi[3] in terms of annualised rate of change in lung function and associated impact on health-related quality of life (HRQoL) to investigate the natural history of abnormal lung function and its impact on HRQoL in a LMIC.

3.6 Materials and methods

3.6.1 Setting and study design

Malawi is one of the world's poorest countries (per capita GDP–$300) and 83% of its 18 million inhabitants live in rural areas[13]. The prevalence of diagnosed COPD and asthma in Malawi is unknown because lung function testing is unavailable out with research settings. Chikwawa (population 360,000) is a predominantly rural district of 4,755 km² in Southern Malawi.

We report the five-year follow-up of a cohort of adult Malawians recruited in 2014. The Chikwawa lung health cohort has been described in detail elsewhere: Njoroge et al[3]. In 2014 a community-based prevalence survey, nested within a cookstove intervention trial, was conducted in accordance with the Burden of Obstructive Lung Disease (BOLD) protocol[3,14]. Participants were randomly sampled from adults living in 50 villages in Chikwawa[3,12]: of the 3000 invited, 1481 participated. Non-participation was usually because of inability to make contact, non-participants were younger and more likely to be male[3,12].

Two rounds of follow-up in 2015 (n=1090) and 2017 (n=989) investigated whether lung function decline was affected by the cook stove intervention or personal air pollution exposures[15]. In 2019, all the participants from 2014 were invited to take part in this five year follow-up.

3.6.2 Ethical considerations

The study was approved by the Imperial College Research Ethics Committee (17IC4272), Liverpool School of Tropical Medicine Research Ethics Committee (19-005) and the Malawi College of Medicine Research and Ethics Committee (COMREC, P·03/19/2617). All participants provided written informed consent.

3.6.3 Data collection

Assessments in 2019 were almost identical to those in 2014, 2015 and 2017 and are described in detail elsewhere[3,12,15]. Interviewer administered questionnaires covered respiratory symptoms, smoking history, environmental exposures, demographics, socio-economic status, and diagnosed respiratory disease[3,12].

Lung function (forced expiratory volume in one second [FEV_1] and forced vital capacity [FVC]) was measured by spirometry (ndd EasyOne Spirometer, ndd Medizintechnik AG, Switzerland), performed before and 15 minutes after 200 µg inhaled salbutamol via spacer. Standard contraindications for spirometry were applied and pregnant women were not tested. The trained and certified spirometry technicians received regular feedback on spirogram quality in accordance with the BOLD protocol[14] and ATS/ERS recommendations[16]. The quality of each spirometry trace was reviewed and scored based on acceptability and repeatability criteria[14,16]. FEV_1 and FVC readings ranked A and B were analysed[16].

The 12–item Short Form Survey (SF–12) (administered in 2014) and the Veterans RAND 12 item survey (VR–12) (administered in 2019) were used to quantify HRQoL from responses to questions on general health perceptions, physical functioning, role limitations due to physical and emotional problems, bodily pain, energy and fatigue, social functioning, and mental health[17,18]. The validated Brazier SF–6D algorithm was applied to obtain a summary preference-based health utility measure (HRQoL utility score) that ranged from 0 (for death) to 1 (full health)[19]. VR–12 responses were mapped to the utility scores from the Brazier SF–6D algorithms to ensure that the scores derived from the SF–12 and VR–12 were comparable. We also assessed the distributional properties of scores obtained from SF–12 and VR–12 tools through the SF–6D algorithms to confirm that they were similar[20,21]. The 2015 and 2017 follow-ups did not include HRQoL.

3.6.4 Statistical considerations

In 2014, a randomized age, sex-stratified sample was identified from lists of adults living in the 50 cookstove trial villages[3,12]. The baseline sample size estimate of 1200[3,12], based on the BOLD protocol[14], resulted in a minimum sample size of 300 in any one age/sex stratum (two age groups: 18–39years, ≥40years) required to approximate an expected prevalence of fixed airflow obstruction of 10–25% with a precision 3·3–5·0%[12]. To compensate for the cookstove trial's clustered design 1481 participants were recruited.

For the current follow-up, sample size estimates were informed by reported rates of FEV_1 decline in US, UK, and Australian cohort studies[22–24]. We estimated the minimum sample required to detect an annual FEV_1 change ≥17ml to be 146 (73 men, 73 women) per year with 90% power, and α=0·05, and included 10% adjustment for attrition and 20% for important covariates in the analysis. Given the five years between 2014 and 2019, the expected difference would be fivefold, we therefore anticipated a minimum of 730 participants (365 men, 365 women) would suffice.

Global Lung Function Initiative (GLI) 2012 reference values for African American ethnicity were used[25]. Absolute FEV_1 and FVC were included as continuous variables in longitudinal analyses. Each participant's spirometry was categorised into patterns consistent with clinical diagnoses: 'normal,' pre-bronchodilator FEV_1 ≥ lower limit of normal (LLN), FVC ≥ LLN, FEV_1/FVC ≥ LLN; 'COPD,' post-bronchodilator FEV_1/FVC < LLN with no/insignificant bronchodilator reversibility; 'asthma,' pre-bronchodilator FEV_1/FVC < LLN and significant reversibility (post-bronchodilator improvement in FEV_1 ≥ 12% and ≥ 200ml); and 'restriction,' post-bronchodilator FVC < LLN, FEV_1/FVC ≥ LLN[9,10].

Primary outcome measures were lung function (FEV_1, FVC) and HRQoL score. Rate of change of FEV_1, and FVC were expressed as ml/year and z-score/year. Rate of change in HRQoL score

associated with changes in the lung function were also estimated. Clinical considerations, analysis of variance and simple linear regression methods identified the following explanatory variables for inclusion in multivariable analysis: follow-up time, age, height, BMI, sex, previous TB diagnosis, smoking, years of schooling, clinical spirometry patterns, reported respiratory diagnoses (any of asthma, emphysema, chronic bronchitis, COPD).

Linear mixed-effects models were used to analyse lung function using all the 2014 and 2019 data. To investigate associations with rate of FEV_1, and FVC, multiplicative terms were individually included in models: time*diagnosed asthma, time*diagnosed COPD, time*previous TB, time*smoking history, time*spirometry consistent with asthma, time*spirometry consistent with COPD, tome*restrictive spirometry. Sensitivity analyses included those participants with lung function from both 2014 and 2019. HRQoL data were only collected in 2014 and 2019. Linear mixed-effects models with robust standard errors were used to analyse HRQoL scores because they have an increasingly skewed distribution[26,27]. Beta regression models with their important explanatory variables were used to conduct sensitivity analysis of HRQoL to assess validity of the mixed-effects model with robust standard errors[28–30]. In all mixed-effects models, random effects were accounted for at the individual level whilst the explanatory fixed-effects were selected sequentially with the optimum model fit by likelihood ratio and deviance testing under maximum likelihood estimation (MLE). Statistical analysis was conducted using R v3·6·0. All significance tests were two-tailed, with $p < 0{\cdot}05$ considered significant.

3.6.5 The regression model structure

The lung function model estimated has the form,

$$Y_{it} = \alpha + \delta_i x_{it} + \beta_1 x_{1t} + \cdots + \beta_i x_{it} + U_i + \mathrm{Z}_{it}\,, i = 1, \ldots, n;\ t = 1, \ldots, m$$

where:

Y_{it} is the dependent variable lung function measurement for participant i, on study cycle t.

α is the y intercept

$\delta_i x_{it}$ is a variable denoting the study cycle, t, for participant i.

$$\beta_1 x_{1t} + \cdots$$

$+ \beta_i x_{it}$ are the β_i coefficient estimates for the explanatory variables x_i at study cycle t.

x_i is given by the explanatory variables such as age, height, previous TB diagnosis and gender.

U_i is the random effect for the ith participant.

Z_{it} are the residuals.

3.7 Results

Between July 2019 and August 2020, 1232 (83%) of the 1481 original participants were assessed. We were unable to follow-up 249: 93 (6·3%) had died, 9 (0·6%) had moved away, 7 (0·5%) were working away, and no information was available for 140 (9·5%). Figure 3-1 outlines participant numbers in each follow-up.

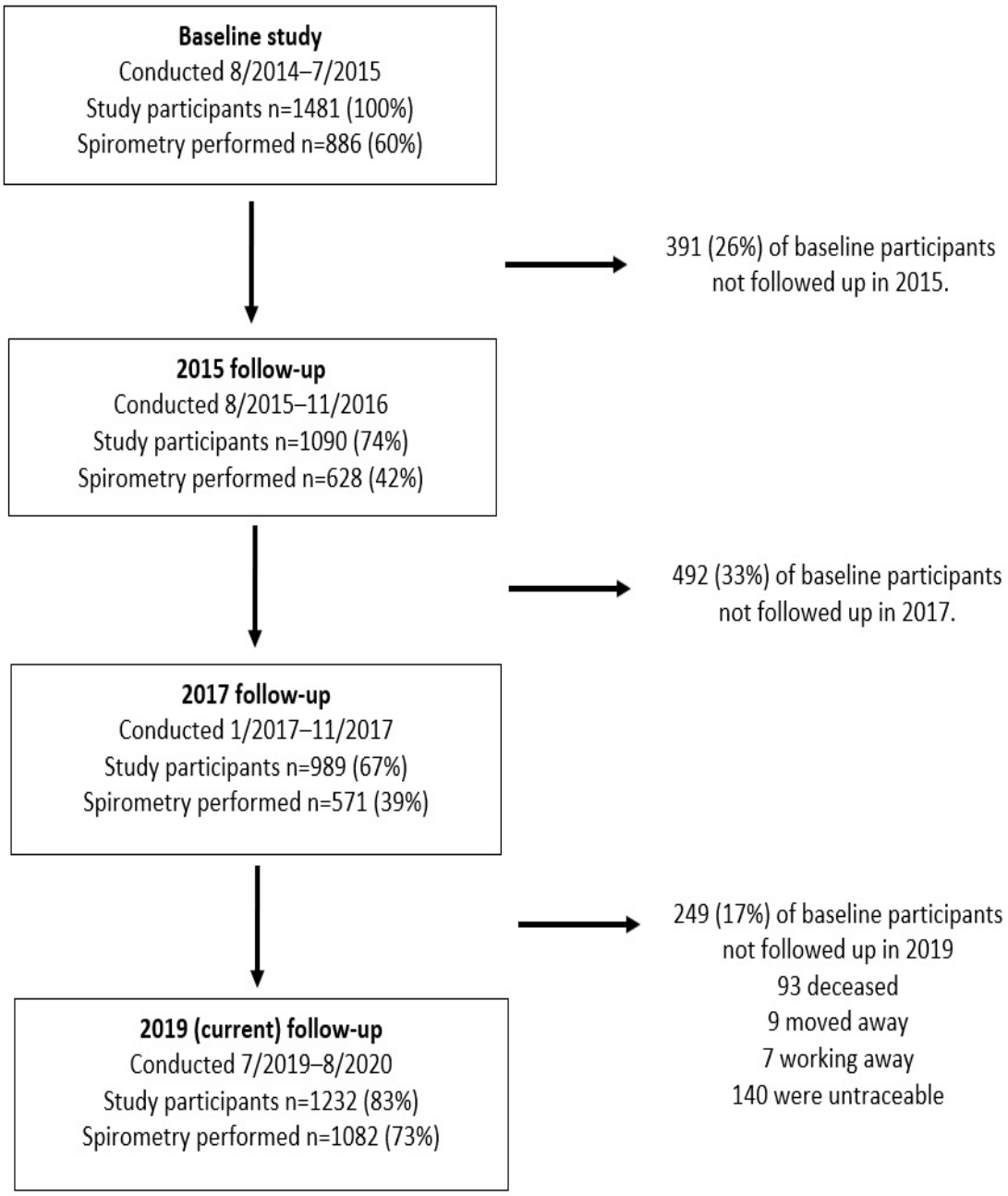

Figure 3-1: Participants in the various follow-up phases of the Chikwawa lung health cohort.

Mean (SD) participant age in 2019 was 49·5 (17·0) years, 278 (23%) had ever smoked, and 724 (59%) were women (Table 3-1). A greater proportion of the 2014 cohort participated in 2019 (n=1232 (83%)) than in 2015 (n=1090 (74%)) or 2017 (n=989 (67%)). Comparison of the 2014 characteristics of those participating or not participating in 2019 (Table 3-2) indicated that those participating in 2019 were older (mean difference [MD] (95% CI): 7·9 years (5·8, 9·9)), less educated (MD: 1·23 years, 0·7, 1·6), less likely to have acceptable spirometry (proportion difference (95% CI): 12·1% (5·5%, 18·7%)), had reduced FEV_1 (MD (95% CI): 3·71%, (0.02%, 7·40%)), and reduced HRQoL score (MD (95% CI): 0·03, (0·02, 0·05)). However, participation in 2019 was not significantly associated with sex, smoking history, respiratory symptoms, or diagnoses.

Table 3-1: Characteristics of study participants at baseline (2014) and 2019.

	Baseline 2014 (n=1481)	**2019 follow-up (n=1232)**
Women, n (%)	844 (57·0%)	724 (58·8%)
Age (years, mean (SD))	43·9 (17.8)	49·5 (17·0)
Grouped age (years), n (%)		
<39	685 (46·3%)	403 (32·7%)
40 – 49	258 (17·4%)	268 (21·8%)
50 – 59	217 (14·7%)	213 (17.3%)
60 – 69	161 (10·9%)	167 (13·6%)
>70	160 (10·8%)	181 (14·7%)
BMI (kg/m^2), mean (SD))	21·6 (3.46)	21·8 (3·93)
BMI, n (%)		
Underweight (< 18.5)	182 (13·9%)	219 (17·8%)
Normal weight (≥18.5; <25.0)	950 (72·8%)	795 (64·4%)
Overweight (≥25.0; <30.0)	133 (10·2%)	161 (13·1%)
Obese (≥ 30.0)	40 (3·1%)	58 (4·7%)
Never smoked	1154 (77·9%)	954 (77·4)
Years of schooling completed, mean (SD)	4·21(4·09)	3·80(3·94)
Highest level of education completed		
None	485 (32·7%)	477 (38·7%)
Primary School	758 (51·2%)	576 (46·8%)
High School	232 (15·7%)	165 (13·4%)
College & University	4 (0·27%)	14 (1·14%)
Unknown	2 (0·14%)	0 (0·00%)

Table 3-2: The 2014 baseline characteristics of study participants who did and did not participate in the 2019 follow-up of the Chikwawa lung health cohort.

2014 outcome	**Participant in 2019 study (n=1232)**	**Did not take part in the 2019 study (n=249)**	**P value**
Women, n(%)	724 (58.8%)	154 (61.8%)	0.41
Age (years, mean (SD)) in 2014	43.4 (17.3)	35.5 (15.3)	<0.0001
BMI (kg/m^2), mean (SD))	21.8 (3.93)	21.6 (2.88)	0.41
Never smoked n (%)	949 (77.4%)	191 (76.7%)	0.98
Years of schooling completed, mean (SD)	4.11 (3.99)	5.34 (4.10)	<0.0001
2014 symptoms			
Any respiratory symptoms, n(%)	166 (13.5%)	26 (10.4%)	0.23
Cough most days, ≥3 months of the year, n(%)	138 (11.2%)	23 (9.2%)	0.44
Usually brings up phlegm from chest, n(%)	32 (2.6%)	5 (2.0%)	0.75
Wheezing/whistling in chest in the past 12 months, n(%)	50 (4.1%)	10 (4.0%)	1.00
Wheezing/whistling in chest in the past 12 months in the absence of a cold, n(%)	19 (1.5%)	1 (0.4%)	0.26
Shortness of breath when hurrying on the level or walking up a slight hill, n(%)	16 (1.3%)	3 (1.2%)	1.00
Breathing problems interfere with usual daily activities, n(%)	39 (3.2%)	7 (2.8%)	0.93
2014 spirometry			
Acceptable spirometry, n(%)	712 (57.8%)	174 (69.9%)	<0.0001
FEV_1, %predicted; mean (SD)	98.8 (21.3)	102.5 (22.4)	0.05
FVC, %predicted; mean (SD)	102.1 (21.9)	104.5 (21.7)	0.19
FEV_1/FVC<LLN n (%)	68 (5.5%)	14 (5.6%)	1.00
FEV_1/FVC< 70%; GOLD definition n(%)	68 (5.5%)	8 (3.2%)	0.18
2014 Quality of life score			
SF-6D derived HRQoL* (mean, (SD))	0.877 (0.128)	0.910 (0.116)	<0.0001

* Health related quality of life

The number of participants providing acceptable spirometry in 2019 (n=1082) was greater than in 2014 (n=886), 2015 (n=628) and 2017 (n=571), while 675 participants had acceptable spirometry in both 2014 and 2019 (Table 3-3).

Table 3-3: Ventilatory function of the participants with acceptable spirometry in 2014 and 2019.

Spirometry	**2014 (n=675)**	**2019 (n=675)**	**p value**
FEV_1, %predicted; mean (SD)	98.4 (16.4)	93.6 (17.1)	<0.001
FVC, %predicted; mean (SD)	101.4 (15.5)	99.1 (17.1)	0.011
FEV_1/FVC; mean % (SD)	80.6% (8.10)	77.5% (9.24)	<0.001
Obstruction			
FEV_1/FVC<LLN n (%)	66 (9.8%)	91 (13.5%)	0.042
FEV_1/FVC<0.70 n(%)	62 (9.2%)	115 (17.0%)	<0.001
Mild: FEV_1≥80% predicted n (%)	38 (5.6%)	62 (9.2%)	<0.001
Moderate: 50%≤FEV_1<80% predicted n (%)	20 (3.0%)	46 (6.8%)	
Severe: 30%≤FEV_1<50% predicted n (%)	3 (0.4%)	6 (0.9%)	
Very severe: FEV_1<30% predicted	1 (0.2%)	1 (0.2)	
Restriction			
FVC <LLN n (%)	28 (4.2%)	47 (7.0%)	0.032

Participants providing acceptable spirometry in 2019 were significantly older, had more years of schooling and were less likely to report coughing, but did not differ significantly for sex, smoking, or symptoms of wheeze, breathlessness or sputum expectoration when compared with participants with no/unacceptable spirometry (Table 3-4).

Table 3-4: 2019 study comparisons of participants with acceptable spirometry and those with no/unacceptable spirometry.

2019 outcome	Acceptable spirometry (n=1082)	No and unacceptable spirometry (n=150)	P value
Women, n(%)	601 (55.5%)	78 (52.0%)	0.465
Age (years, mean (SD))	49.3 (16.4)	59.1 (12.6)	<0.001
BMI (kg/m^2), mean (SD))	21.7 (3.89)	21.6 (3.84)	0.673
Never smoked	835 (77.2%)	106 (70.7%)	0.098
Years of schooling completed, mean (SD)	3.85 (3.96)	2.74 (3.43)	<0.001
Symptoms			
Any respiratory symptoms, n(%)	304 (28.1%)	38 (25.3%)	0.541
Cough on most days ≥3 months of the year, n(%)	255 (23.6%)	37 (67.3%)	<0.001
Usually brings up phlegm from chest, n(%)	109 (10.0%)	10 (6.7%)	0.239
Wheezing/whistling in chest in the past 12 months, n(%)	67 (6.2%)	5 (3.3%)	0.225
Wheezing/whistling in chest in the past 12 months in the absence of a cold, n(%)	47 (4.3%)	4 (2.7%)	0.455
Shortness of breath when hurrying on the level or walking up a slight hill, n(%)	56 (5.2%)	5 (3.3%)	0.439
Breathing problems interfere with usual daily activities, n(%)	33 (3.0%)	3 (2.0%)	0.648
Quality of life score			
SF-6D derived HRQoL (mean, (SD))	0.798 (0.110)	0.798 (0.103)	0.979

3.7.1 Symptoms

There was an increase in reported respiratory symptoms between 2014 and 2019 (Table 3-5); the proportion difference (95% CI) for 'any respiratory symptom' was 14·7% (11·6%, 17·8%); 'cough' 12·5% (9·6%, 15·5%); 'sputum expectoration' 7·8% (5·8%, 9·7%); 'wheezing' 5·3% (3·7%, 7·0%); 'dyspnoea' 4·0% (2·5%, 5·6%). Participants also reported more diagnosed asthma, emphysema, or COPD 2·8 % (1·0%, 4·6%) and previous TB 3·8% (2·1%, 5·6%). Restricting analysis to participants providing respiratory symptom data in both 2014 and 2019 made little difference to the magnitude of the observed differences (Table 3-6).

Table 3-5: Changes in symptom prevalence, diagnosed respiratory disease and lung function between 2014 and 2019.

	Baseline 2014 (n=1481)	**2019 follow-up (n=1232)**
Symptoms		
Any respiratory symptoms, n (%)	203 (13·7%)	350 (28·4%)
Cough most days of the month for ≥3 months of the year, n (%)	167 (11·3%)	294 (23·8%)
Usually brings up phlegm from chest, n (%)	39 (2·6%)	128 (10·4%)
Wheezing/whistling in chest in the past 12 months, n (%)	63 (4·3%	85 (6·9%)
Wheezing/whistling in chest in the past 12 months in the absence of a cold, n (%)	24 (1·6%)	60 (4·9%)
Shortness of breath when hurrying on the level or walking up a slight hill, n (%)	23 (1·6%)	69 (5·6%)
Breathing problems interfere with usual daily activities, n (%)	44 (3·0%)	44 (3·6%)
Diagnosed lung disease		
Diagnosed asthma, n (%)	51 (3·4%)	56 (4·5%)
Diagnosed COPD, n (%)	1 (0·1%)	11 (0·9%)
Diagnosed asthma, emphysema, chronic bronchitis, or COPD, n (%)	59 (4·0%)	84 (6·8%)
Previous TB, n (%)	47 (3·2%)	87 (7·0%)
Spirometry	*(n=886)*	*(n=1082)*
FEV_1, %predicted; mean (SD)	97·8% (16·8%)	91·8% (19·3%)
FVC, %predicted; mean (SD)	101% (15·6%)	98·8% (19·8%)
FEV_1/FVC; mean % (SD)	80.5% (8·5%)	76·1% (11·0%)
Obstruction		
FEV_1/FVC<LLN n (%)*	84 (9·5%)	189 (17·5%)
FEV_1/FVC<0.70 n (%)	82 (9·3%)	232 (21·4%)
Mild: FEV_1≥80% predicted n (%)	47 (5·3%)	106 (9·8%)
Moderate: 50%≤FEV_1<80% predicted n (%)	26 (2·9%)	103 (9·5%)
Severe: 30%≤FEV_1<50% predicted n (%)	8 (0·9%)	17 (1·6%)
Very severe: FEV_1<30% predicted	1 (0·1%)	6 (0·6%)
Restriction		
FVC <LLN n (%)	44 (5·0%)	91 (8·4%)
Spirometry clinical pattern		
Normal	702 (79·2%)	748 (68·2%)
COPD*	61 (6·9%)	134 (12·4%)
Asthma	23 (2·6%)	40 (3·7%)
Restriction	34 (3·8%)	52 (4·8%)
Unclassified not normal spirometry pattern	66 (7·4%)	108 (10·0%)

*Discrepancy reflect differences numbers for those with acceptable post-bronchodilator spirometry and those with acceptable pre and post bronchodilator spirometry

Table 3-6: Changes in symptom prevalence and diagnosed respiratory disease in those with data in both 2014 and 2019.

	Baseline 2014 (n=1232)	**2019 follow-up (n=1232)**	**P value**
Symptoms			
Any respiratory symptoms, n (%)	166 (13.5%)	350 (28·4%)	<0.0001
Cough on most days ≥3 months of the year, n (%)	138 (11.2%)	294 (23·8%)	<0.0001
Usually brings up phlegm from chest, n (%)	32 (2.6%)	128 (10·4%)	<0.0001
Wheezing/whistling in chest in the past 12 months, n (%)	50 (4.1%)	85 (6·9%)	0.0026
Wheezing/whistling in chest in the past 12 months in the absence of a cold, n (%)	19 (1.5%)	60 (4·9%)	<0.0001
Shortness of breath when hurrying on the level or walking up a slight hill, n (%)	16 (1.3%)	69 (5·6%)	<0.0001
Breathing problems interfere with usual daily activities, n (%)	39 (3.2%)	44 (3·6%)	0.6551
Diagnosed lung disease			
Diagnosed asthma, n (%)	42 (3.4%)	56 (4·5%)	0.1802
Diagnosed COPD, n (%)	1 (0.1%)	11 (0·9%)	0.0092
Diagnosed asthma, emphysema, chronic bronchitis, or COPD, n (%)	50 (4.1%)	84 (6·8%)	0.0034
Previous TB, n (%)	37 (3.0%)	87 (7·0%)	<0.0001

3.7.2 Lung function changes

Comparison of spirometry data between 2014 and 2019 indicated that the unadjusted annual rate of FEV_1 decline was 73·4 ml/year (95% CI): (61·0, 85·6; p<0·0001) and for FVC 60·1 ml/year (46·0, 74·2; p<0·0001) (Figure 3-2). When expressed as percent predicted and z-scores (Table 3-7) the rate of FEV_1 decline exceeded that of FVC and that predicted by GLI-2012. These rates of decline were reflected in the clinical patterns of lung function such that in 2019 a higher proportion had spirometry consistent with COPD (predominantly mild to

moderate), however between 2014 and 2019 there was little difference in the proportion of participants with spirometry consistent with asthma and pure restriction (Table 3-4).

Table 3-7: Changes in ventilatory function between 2014 and 2019 expressed as GLI-2012 z-scores.

	Baseline 2014 n=1481	**2019 follow-up n=1232**	**p value**
z-scores			
FEV_1 z-score; mean, (SD)	-0.140 (1.157)	-0.527 (1.275)	<0.001
FVC z-score; mean, (SD)	0.039 (1.091)	-0.135 (1.310)	0.001
FEV_1/FVC z-score; mean, (SD)	-0.328 (0.996)	-0.663 (1.199)	<0.001
FEV_1/FVC<LLN n (%)	84 (9.5%)	189 (17.5%)	<0.001
FVC<LLN n (%)	44 (5.0%)	91 (8.4%)	0.004

Unadjusted annual decline in:

- FEV_1 z-score was 0.077(95% CI): (0.056, 0.099; p<0.001)
- FVC z-score 0.035 (95% CI): (0.013, 0.056; p=0.002).

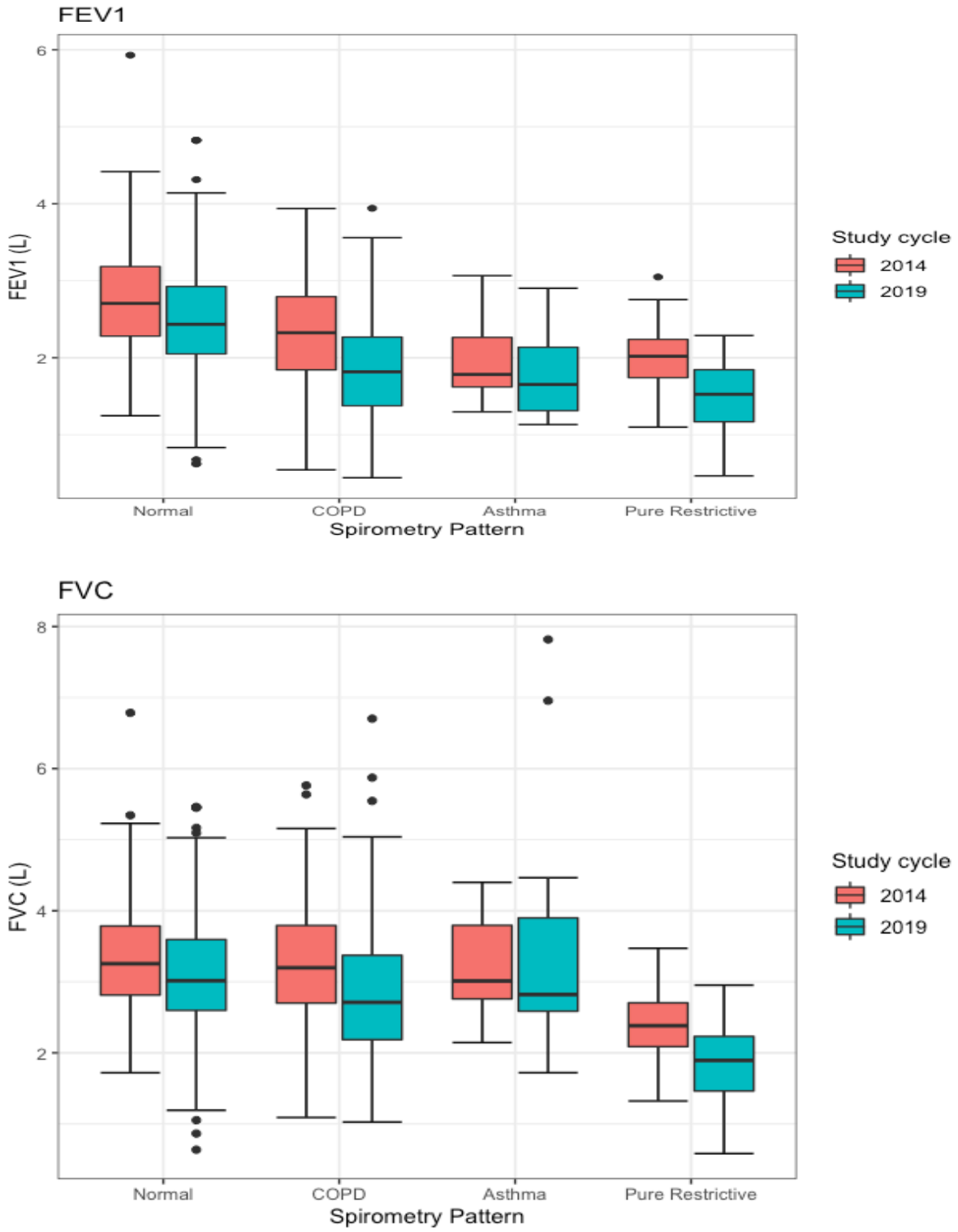

Figure 3-2: FEV_1 and FVC box and whisker plots for participants grouped into clinical respiratory diagnoses by their spirometry. Each boxplot shows the variation in the lung function measures within each spirometry diagnosis. Scatter points are outlier values. Upper

whisker shows Q3 (75th percentile) plus 1.5*Interquartile range (IQR). Lower whisker shows Q1 (25th percentile) minus 1.5*IQR.

The lung function characteristics of participants with acceptable spirometry in both 2014 and 2019 (n=675) and for those with data in 2014, 2015, 2017 and 2019 (n=276) are presented in Table 3-3 & Table 3-8. In the 276 participants with acceptable spirometry in all four study phases, FEV_1 declined by 55·2 ml/year (95% CI: 34·6, 75·8; p < 0·0001) and FVC by 47·2 ml/year (22·6, 72·0; p < 0·0001).

Table 3-8: Ventilatory function of the participants with acceptable spirometry in 2014, 2015, 2017 and 2019.

Spirometry	**2014 (n=276)**	**2015 (n=276)**	**2017 (n=276)**	**2019 (n=276)**	**p value$^{\Psi}$**
FEV_1, %predicted; mean (SD)	97.4 (13.9)	100 (16.1)	97.5 (13.8)	93.6 (17.1)	0.003
FVC, %predicted; mean (SD)	99.5 (13.9)	102 (15.9)	99.4 (13.4)	97.5 (14.9)	0.106
FEV_1/FVC; mean % (SD)	81.6% (6.55)	82.0 (8.85)	81.4 (7.14)	78.7 (7.43)	<0.001
Obstruction					
FEV_1/FVC<LLN n (%)	16 (5.8%)	21 (7.6%)	22 (8.0%)	31 (11.2%)	0.033
FEV_1/FVC<0.70 n(%)	14 (5.1%)	18 (6.5%)	19 (6.9%)	34 (12.3%)	0.004
Mild: FEV_1≥80% predicted n (%)	9 (3.3%)	13 (4.7%)	13 (4.7%)	19 (6.9%)	
Moderate: 50%≤FEV_1<80% predicted n (%)	5 (1.8%)	5 (1.8%)	6 (2.2%)	14 (5.1%)	
Severe: 30%≤FEV_1<50% predicted n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	
Very severe: FEV_1<30% predicted	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Restriction					
FVC<LLN n (%)	13 (4.7%)	13 (4.7%)	10 (3.6%)	19 (6.9%)	0.363

$^{\Psi}$ 2019 vs 2014

Unadjusted annual decline in:

- FEV_1 z-score was 0.057(95% CI): (0.022, 0.092; p=0.002)
- FVC z-score 0.036 (95% CI): (0.002, 0.071; p=0.039)

3.7.2.1 Mixed effect model – lung function changes

In the mixed-effects regression model (Table 3-9) of all participants with acceptable spirometry in 2014 and/or 2019 (model 1), adjusted FEV_1 declined by 53·4 ml/year (95% CI): (49·0, 57·8; p < 0·0001) and FVC by 45·2 ml/year (39·2, 50·5; p < 0·0001). Reduced FEV_1 and FVC were significantly associated with age (FEV_1 p < 0·001; FVC p < 0·001) , female sex (FEV_1 p < 0·001; FVC p < 0·001), reducing height (FEV_1 p < 0·001; FVC p < 0·001), reducing BMI (FEV_1 p < 0·001; FVC p < 0·004), but not smoking history (FEV_1 p = 1; FVC p = 0·803) or years of schooling (FEV_1 p = 1; FVC p = 0·251) . Reported previous TB was associated with reduced FEV_1 (p < 0·001) and FVC (p < 0·001), whereas reported diagnosed asthma was associated with reduced FEV_1 (p < 0·014) but not FVC, (p < 0·453), a reported diagnosis of emphysema (FEV_1 p = 1; FVC p = 1), chronic bronchitis (FEV_1 p = 1; FVC p = 1), or COPD (FEV_1 p = 0·830; FVC p = 0·485) was not associated with FEV_1 or FVC. When compared to those with normal lung function, spirometry patterns consistent with COPD or restriction were associated with reduced FEV_1 (p < 0·001) and FVC (p < 0·001) and spirometry consistent with asthma was associated with reduced FEV_1 (p < 0·001) but not FVC (p < 0·260). None of the included interaction terms were significantly associated with FEV_1 or FVC indicating that rates of FEV_1 and FVC decline were not associated with diagnosed asthma (FEV_1 p = 0·429; FVC p = 0·619), previous TB (FEV_1 p = 0·091; FVC p = 0·092), smoking history (FEV_1 p = 0·910; FVC p = 0·108) or spirometry consistent with asthma (FEV_1 p = 0·731; FVC p = 0·160), COPD (FEV_1 p = 0·900; FVC p = 0·977), or restriction (FEV_1 p = 0·502; FVC p = 0·531). Inclusion of height-squared and cookstove intervention allocation status between 2014 and 2015 in the models revealed no associations between cookstove intervention or height squared on FEV_1, FVC or their state of decline. A sensitivity analysis of participants with acceptable spirometry in both 2014 and 2019 (model 2) indicated that adjusted FEV_1 declined by 46·1 ml/year (95% CI): (22·7, 69·0;

p<0·0001) and FVC by 42·4 ml/year (37·7, 47·0; p<0·0001). The parameter estimates for FEV_1 and FVC z-scores are presented in Table 3-10.

Table 3-9: Linear Mixed Effects Modelling applied to FEV1 and FVC data from participants in 2014 and 2019, statistically significant associations.

	FEV_1 (ml)		**FVC (ml)**	
	Model 1[$$] Estimate (95% CI)	**Model 2[££] Estimate (95% CI)**	**Model 1[$$] Estimate (95% CI)**	**Model 2[££] Estimate (95% CI)**
Time to follow-up (per year)	-53·5 (-57·8, -49·0)	-46·1 (-69·0, -22·7)	-45·2 (-50·5, -39·2)	-42·4 (-47·0, -37·7)
Age (per year)	-16·2 (-17·3, -15·0)	-15·6 (-17·0, -13·9)	-10·2 (-11·7, -8·6)	-9·3 (-11·1, -7·3)
Height (per cm)	26·4 (24·0, 29·2)	25·2 (22·2, 28·1)	34·1 (30·6, 37·6)	32·2 (28·3, 36·0)
Sex (female)	-465 (-513, -420)	-488 (-542, -433)	-630 (-686, -569)	-642 (-714, -573)
BMI (per kg/m^2)	12.3 (7.2, 17.3)	12.6 (6.0, 18.1)	9.5 (2.4, 15.8)	8.8 (1.0, 16.5)
Previous TB	-213 (-295, -140)	-198 (-292, -105)	-174 (-276, -84·5)	-189 (-313, -76·1)
Diagnosed asthma	-113 (-196, -32·7)	-123 (-214, -32·7)		
Clinical spirometry pattern (compared to normal)				
COPD	-386 (-428, -346)	-324 (-374, -279)	-146 (-196, -94·4)	-88·9 (-146, -27·9)
Asthma	-627 (-754, -491)	-497 (-669, -312)		
Restriction	-691 (772, -612)	-673 (-773, -753)	-813 (-911, -705)	-754 (-877, -627)

[$$] Models 1 include FEV_1 and FVC data from all the participants with acceptable spirometry in 2014 (n=886) and/or 2019 (n=1082).

[££] Models 2, sensitivity analysis, include FEV_1 and FVC data from participants with acceptable spirometry in 2014 and 2019 (n=675).

TB, Tuberculosis; BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second.

FEV_1 model: 88% of the variability of FEV_1 accounted for in the final mixed-effects regression model of which fixed-effects accounts for 70% of the variation.

FVC model: 86% of the variability of FVC accounted for in the final mixed-effects regression model of which fixed-effects accounts for 62% of the variation.

Table 3-10: Linear Mixed Effects Modelling applied to FEV1 and FVC data expressed as z-scores from participants in 2014 and 2019, statistically significant associations.

	FEV_1 (z-score)		**FVC (z-score)**	
	Model 1[$$] Estimate (95% CI)	**Model 2[ff] Estimate (95% CI)**	**Model 1[$$] Estimate (95% CI)**	**Model 2[ff] Estimate (95% CI)**
Time to follow-up (Per year)	-0.068 (-0.084, -0.053)	-0.061 (-0.077, -0.045)	-0.033 (-0.049, -0.017)	-0.033 (-0.049, -0.017)
Age (per year)	0.012 (0.008,0.015)	0.014 (0.010, 0.018)	0.018 (0.014, 0.021)	0.019 (0.015, 0.023)
Height (per cm)	-0.018 (-0.026, -0.011)	-0.024 (-0.032, -0.015)	-0.025 (-0.033, -0.018)	-0.031 (-0.039, -0.022)
Sex (female)	0.379 (-0.505, -0.250)	-0.424 (-0.568, -0.274)	-0.468 (-0.595, -0.325)	-0.510 (-0.675, -0.359)
BMI (per kg/m^2)	0.032 (0.017,0.046)	0.034 (0.0179,0.051)	0.018 (0.003, 0.032)	0.019 (0.001, 0.037)
Previous TB	-0.586 (-0.810, -0.386)	-0.596 (-0.864, -0.316)	-0.405 (-0.629, -0.182)	-0.447 (-0.723, -0.181)
Diagnosed asthma	-0.286 (-0.500, -0.075)	-0.333 (-0.569, -0.073)		
Clinical spirometry pattern (Compared to normal)				
COPD	-1.045 (-1.159, -0.928)	-0.881 (-1.016, -0.744)	-0.356 (-0.471, -0.246)	-0.234 (-0.375, -0.106)
Asthma	-1.568 (-1.926, -1.236)	-1.238 (-1.722, -0.707)		
Restriction	-1.927 (-2.145, -1.725)	-1.822 (-2.076, -1.556)	-2.033 (-2.234, -1.753)	-1.816 (-2.111, -1.511)

[$$] Models 1 include FEV_1 and FVC data from all the participants with acceptable spirometry in 2014 (n=886) and/or 2019 (n=1082).

[ff] Models 2, sensitivity analysis, include FEV_1 and FVC data from participants with acceptable spirometry in 2014 and 2019 (n=675).

TB, Tuberculosis; BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second.

FEV_1 z-score model: 66% of the variability of FEV_1 accounted for in the final mixed-effects regression model of which fixed-effects accounts for 29% of the variation.
FVC z-score model: 65% of the variability of FVC accounted for in the final mixed-effects regression model of which fixed-effects accounts for 24% of the variation.

3.7.3 Changes in health-related quality-of-life

Between 2014 and 2019 there was a significant decline in unadjusted mean (SD) HRQoL utility score from 0·873 (0·133) to 0·790 (0·116) ($p < 0·0001$) and the proportion reporting perfect health (score of 1) declined from 39% (n=582) to 2% (n=23) (Figure 3-3). Reduced HRQoL in 2014 and 2019 was associated with reported respiratory symptoms and previously diagnosed TB in those with acceptable spirometry (Table 3-11).

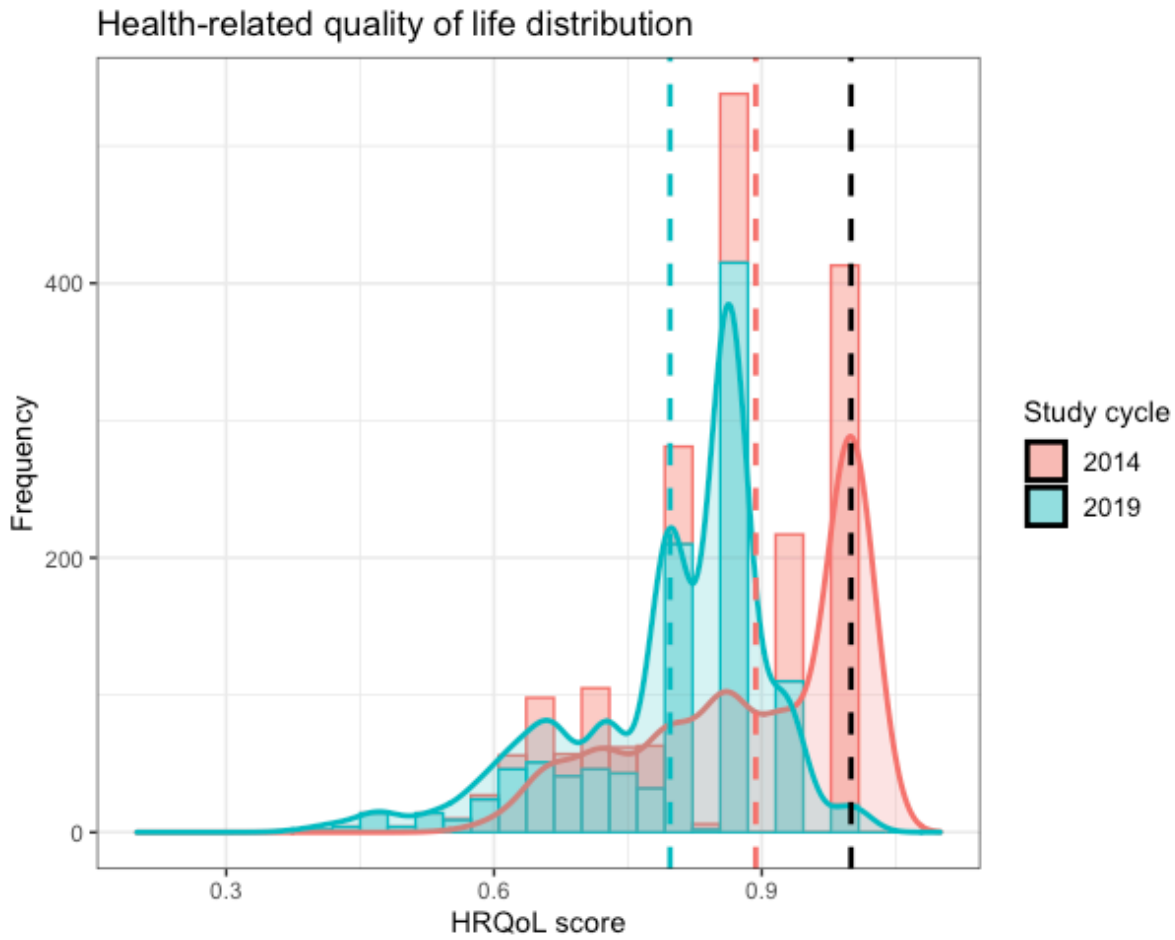

Figure 3-3: Histograms with their overlaid kernel density plot (solid line) of the HRQoL scores of all the participants in 2014 and 2019 (range 0 – 1). The coloured dashed lines are the mean value in each follow-up study while the black dashed line shows an HRQoL score of 1 (perfect health).

Table 3-11: HRQoL scores of participants in 2014 and 2019 associations with respiratory symptoms and diagnosed respiratory diseases for those with acceptable spirometry.

	2014			2019		
	HRQOL score mean, SD			HRQOL score mean, SD		
	Yes	No	p value	Yes	No	p value
Symptoms						
Any respiratory symptoms.	0.831 (0.123) (n=113)	0.907 (0.111) (n=719)	<0.001	0.764 (0.127) (n=304)	0.811 (0.100) (n=778)	<0.001
Cough ≥3 months of the year	0.838 (0.125) (n=87)	0.899 (0.116) (n=797)	<0.001	0.770 (0.123) (n=255)	0.807 (0.104) (n=827)	<0.001
Usually brings up phlegm from chest	0.815 (0.132) (n=23)	0.895 (0.117) (n=863)	0.009	0.747 (0.143) (n=109)	0.804 (0.104) (n=973)	<0.001
Wheezing/whistling in chest in the past 12 months, n(%)	0.809 (0.136) (n=32)	0.896 (0.116) (n=852)	0.001	0.697 (0.142) (n=67)	0.805 (0.104) (n=1015)	<0.001
Wheezing in the past 12 months in the absence of a cold	0.811 (0.126) (n=11)	0.894 (0.118) (n=873)	0.054	0.688 (0.142) (n=47)	0.803 (0.106) (n=1035)	<0.001
Shortness of breath when hurrying on the level or walking up a slight hill.	0.793 (0.113) (n=11)	0.901 (0.114) (n=875)	0.010	0.694 (0.121) (n=56)	0.803 (0.106) (n=1026)	<0.001
Breathing problems interfere with usual daily activities.	0.818 (0.143) (n=24)	0.895 (0.117) (n=862)	0.015	0.684 (0.166) (n=33)	0.801 (0.106) (n=1049)	<0.001
Diagnosed lung disease						
Diagnosed asthma.	0.856 (0.132) (n=29)	0.895 (0.118) (n=857)	0.129	0.770 (0.139) (n=48)	0.799 (0.108) (n=1034)	0.155
Diagnosed, emphysema, chronic bronchitis, or COPD.	0.871 (0.130) (n=33)	0.894 (0.118) (n=853)	0.321	0.758 (0.142) (n=68)	0.801 (0.107) (n=1014)	0.017
Previous TB	0.834 (0.112) (n=22)	0.895 (0.118) (n=864)	0.020	0.749 (0.150) (n=76)	0.802 (0.106) (n=1006)	0.004

In the entire cohort, diagnosed emphysema, chronic bronchitis or COPD was associated with reduced HRQoL in 2019 but not 2014, diagnosed asthma was not associated with HRQoL (Table 3-11). Spirometry consistent with asthma was associated with reduced HRQoL (MD, (95% CI): 0·080 (0·021, 0·131; p=0·0029), as was spirometry consistent with COPD (0·037, [0·020, 0.055, p<0·0001]) and pure restriction (0·055, [0·020, 0·089, p=0·0003]) (Figure 3-4).

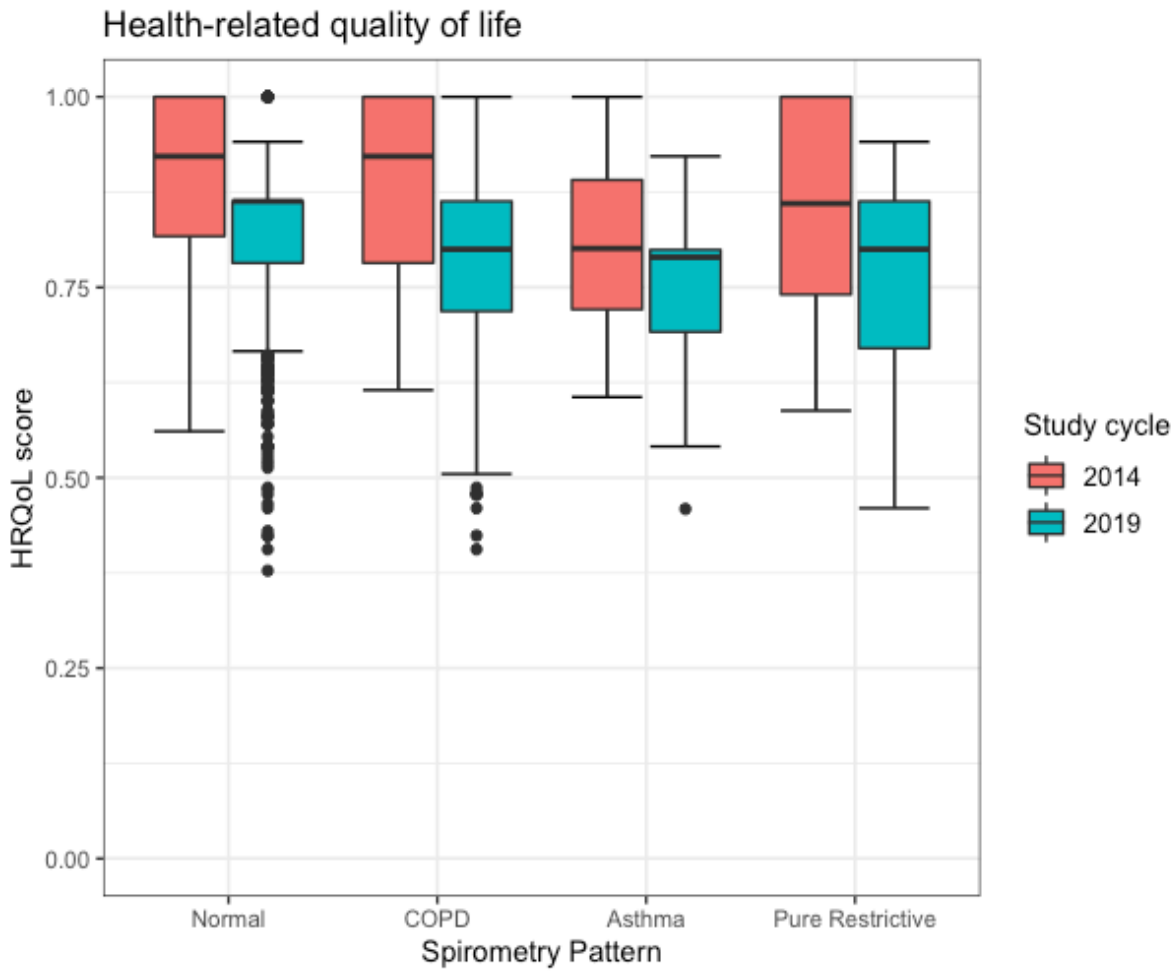

Figure 3-4: Box and whisker plots of HRQoL in relation to spirometric patterns of respiratory disease in 2014 and 2019. HRQoL scores range 0 – 1. Scatter points are outlier values. Upper whisker shows Q3 (75th percentile) plus 1.5*Interquartile range (IQR). Lower whisker shows Q1 (25^{th} percentile) minus 1.5*IQR

Table 3-12: HRQoL scores of participants in 2014 and 2019 associations with respiratory symptoms and diagnosed respiratory diseases.

	2014			2019		
	HRQOL score mean, (SD)			HRQOL score mean, (SD)		
	Yes	No	p value	Yes	No	p value
Symptoms						
Any respiratory symptoms·	0·805 (0·138) (n=203)	0·894 (0·122) (n=1163)	<0·001	0·752 (0·133) (n=350)	0·804 (0·100) (n=882)	<0·001
Cough ≥3 months of the year	0·811 (0·141) (n=167)	0·880 (0·130) (n=1314)	<0·001	0·758 (0·130) (n=294)	0·800 (0·109) (n=938)	<0·001
Usually brings up phlegm from chest	0·788 (0·153) (n=39)	0·874 (0·132) (n=1442)	0·009	0·731 (0·145) (n=128)	0·796 (0·110) (n=1104)	<0·001
Wheezing/whistling in chest in the past 12 months, n (%)	0·790 (0·147) (n=63)	0·876 (0·131) (n=1418)	<0·001	0·683 (0·142) (n=85)	0·797 (0·104) (n=1147)	<0·001
Wheezing in the past 12 months in the absence of a cold	0·789 (0·130) (n=24)	0·874 (0·133) (n=1457)	0·004	0·676 (0·140) (n=60)	0·795 (0·111) (n=1172)	<0·001
Shortness of breath when hurrying on the level or walking up a slight hill.	0·759 (0·130) (n=23)	0·888 (0·123) (n=1310)	<0·001	0·687 (0·124) (n=69)	0·796 (0·112) (n=1163)	<0·001
Breathing problems interfere with usual daily activities.	0·792 (0·151) (n=44)	0·875 (0·132) (n=1437)	0·001	0·669 (0·160) (n=44)	0·794 (0·112) (n=1188)	<0·001
Diagnosed lung disease						
Diagnosed asthma·	0·824 (0·140) (n=51)	0·874 (0·132) (n=1430)	0·014	0·754 (0·149) (n=56)	0·791 (0·114) (n=1176)	0·069
Diagnosed, emphysema, chronic bronchitis, or COPD.	0·827 (0·142) (n=59)	0·874 (0·132) (n=1422)	0·013	0·727 (0·154) (n=84)	0·794 (0·111) (n=1148)	<0·001
Previous TB	0·806 (0·142) (n=47)	0·875 (0·132) (n=1434)	0·002	0·733 (0·152) (n=87)	0·794 (0·111) (n=1145)	<0.001

3.7.3.1 Mixed effect model – Changes in health-related quality-of-life

In the mixed-effects regression model (Table 3-13) reduced HRQoL was associated with time ($p < 0{\cdot}001$), older age at baseline ($p < 0{\cdot}001$) and female sex ($p < 0{\cdot}001$) but not years of schooling ($p = 0{\cdot}807$) or smoking ($p < 0{\cdot}085$). The symptoms of dyspnoea, wheeze, and cough were independently associated with reduced HRQoL, with dyspnoea appearing to be of greatest magnitude and cough the least. Reduced HRQoL was associated with previous TB, but not diagnosed asthma, emphysema, chronic bronchitis, or COPD. HRQoL was beneficially associated with FEV_1 %predicted but not FVC. There were no significant interactions between time and diagnosed conditions (diagnosed asthma $p = 0{\cdot}714$; diagnosed COPD $p= 0{\cdot}221$; previous TB $p = 0{\cdot}876$) or spirometric patterns (spirometry consistent with COPD $p = 0{\cdot}646$; spirometry consistent with asthma $p = 0{\cdot}409$; spirometry consistent with restriction $p = 0{\cdot}204$). In the sensitivity analysis results from a beta regression model, all the previous associations and inferences persisted apart from previously diagnosed TB that was no longer significantly associated.

Table 3-13: Robustly fit linear mixed effects modelling applied to HRQoL data from participants in 2014 and 2019.

	HRQoL[$$]			
	Model A (Symptoms + spirometry clinical pattern)		**Model B (Symptoms + spirometry)**	
	Estimate (95% CI)	P value[Ψ]	Estimate (95% CI)	p value[Ψ]
Time to follow-up (2019 vs 2014)[a]	-0·083 (-0·093, -0·073)	<0·001	-0·081 (-0·091, -0·071)	<0·001
Age group[b]				
40-49 years	-0·002 (-0·014, 0·011)	0·819	-0·003 (-0·015, 0·010)	0·670
50-59 years	-0·023 (-0·037, -0·009)	0·001	-0·026 (-0·040, -0·011)	<0·001
60-69 years	-0·020 (-0·036, -0·004)	0·013	-0·022 (-0·038, -0·006)	0·006
≥70 years	-0·074 (-0·092, -0·056)	<0·001	-0·079 (-0·098, -0·060)	<0·001
Sex (female)	-0·032 (-0·041, -0·022)	<0·001	-0·031 (-0·041, -0·021)	<0·001
Symptoms				
Cough ≥3 months of the year	-0·023 (-0·037, -0·009)	0·001	-0·023 (-0·037, -0·010)	0·001
Usually brings up phlegm from chest	-0·021 (-0·042, 0·001)	0·058	-0·021 (-0·042, 0·000)	0·047
Wheezing in the past 12 months in the absence of a cold	-0·062 (-0·087, -0·036)	<0·001	-0·062 (-0·088, -0·036)	<0·001
Shortness of breath when hurrying on the level or walking up a slight hill	-0·093 (-0·119, -0.066)	<0·001	-0·091 (-0·117, -0·064)	<0·001
Diagnoses				
Previous TB	-0·032 (-0·055, -0·009)	0·006	-0·026 (-0·049, -0·003)	0·028
Spirometry pattern [c, &]				
COPD	-0·009 (-0.021, 0.003)	0·152		

Asthma	-0·040 (-0·080, -0·001)	0·047		
Restrictive	-0·037 (-0·059, -0·013)	0·002		
Spirometry				
FEV_1 % predicted (per %)			0·0005 (0·000, 0·001)	0·034
FVC % predicted (per %)			0·0004 (-0·0003, 0·001)	0·583

Ψ Significance was determined using Satterthwaite approximations of degrees of freedom[31]. Reference Category: [a] Baseline study. [b] <40 years. [c] Normal spirometry pattern

[&] The spirometry pattern variable was added into the model instead of FEV_1 variable

$$ Models include HRQoL data from all the participants with acceptable spirometry (2014 n=886, 2019 n=1082).

3.8 Discussion

In this first longitudinal study of HRQoL in relation to ventilatory function and chronic respiratory disease in sub-Saharan Africa, we report adjusted annual rates of FEV_1 and FVC decline of 53·4 ml/year (95% CI: 49·0, 57·8) and 45·2 ml/year (39·2, 50·5), respectively. More robust estimates of FEV_1 and FVC decline from those participants in both 2014 and 2019, were 46·1 ml/year (22·7, 69·0) and 42·4 ml/year (37·7, 47·0), respectively. These rates of decline were reflected in an increase in spirometry consistent with COPD from 9·5% (7·6%, 11·6%) in 2014 to 17·5% (15·3%, 19·9%) in 2019. In the same period diagnosed COPD increased from 0·1% (0, 0·4%) to 0·9% (0·5%, 1·6%). There was no change in reported diagnosis of asthma or in spirometry consistent with asthma or pure restriction. The second main finding was that HRQoL was adversely and independently associated with the symptoms of dyspnoea, wheeze, and cough, previously diagnosed TB, and declining FEV_1.

The annual rate of FEV_1 decline of 46–53 ml/year in this cohort is greater than the 'normal' 24–29 ml/year decline reported in healthy non-smokers in high income countries (HICs), but similar to the 40–55ml/year decline in smokers of ≥15 cigarettes/day in HICs, and the 53 ml/year reported in an accelerated FEV_1 decline trajectory group accounting for 48% of observed COPD in three US and European cohorts[22,32]. The cause(s) of the relatively rapid rate of FEV_1 decline in Malawian adults is unclear. Although comparable to smoking 15 cigarettes/day in HICs, smoking is unlikely to underlie the observed decline in the general Malawian population because only 14% of participants currently smoked, with most smoking a few cigarettes a day. Previous studies of this cohort have reported no association between lung function (or rate of decline) and smoking status, cookstove intervention and personal pollution exposure ($PM_{2.5}$, CO)[15], similar to the findings from our analysis. The relatively rapid rate of FEV_1 decline may be a result of frequent pulmonary infections consequent upon

genetic factors and/or dietary factors. Reduced FEV_1 (but not rate of decline) was associated with diagnosed asthma, previous TB, and spirometry consistent with COPD, asthma and restriction, suggesting that most of the differences in lung function occurred prior cohort set up and were not a consequence of differential rates of FEV_1 decline during follow-up. This finding is consistent with reports from cohort studies in HICs that reductions in FEV_1 in later adult life observed in COPD and asthma are largely a consequence of the tracking of suboptimal lung function from childhood into adulthood[23,24,33]. For those with a previous diagnosis of TB we speculate that the observed differences reflect the tracking of reduced lung function consequent upon well recognised, largely irreversible fibrotic processes associated with TB[34].

The 2015 and 2017 follow-ups of this cohort reported an FEV_1 decline of 30·9ml/year (21·6, 40·1) and for FVC 38·3ml/year (28·5, 48·1), comparable with the natural age-related decline reported in non-smokers in Europe/USA[15,22,32]. The most likely explanation for the disparity between the 2015/7 and 2019 follow-up (30·9 vs 53·4ml/year) is the greater number participants with acceptable spirometry in 2019 (n=1082) compared with 2014 (n=886), 2015 (n=628) and 2017 (n=571). It is likely that the 53·4ml/year rate of decline reported here is an over-estimate resulting from participants providing spirometry in 2019, but not 2014, who were older, current smokers and symptomatic. The analysis of participants with acceptable spirometry in both 2014 and 2019 supports this notion, even so the rate of FEV_1 decline of 46·1 ml/year (22·7, 69·0) is still cause for concern. We did not observe the high rates of restriction reported in urban Malawi (38·6%) and the 2014 baseline study of this cohort (34·8%)[12], probably reflecting the use of NHANES III predictive equations for white Americans whereas we used African American GLI–2012 predictive equations as recommended by ATS/ERS[16].

Our findings on HRQoL as adversely and independently associated with age, female sex, respiratory symptoms (dyspnoea, wheeze, cough), previous TB, declining FEV_1 and spirometry consistent with asthma or pure restriction are consistent with other studies. A cross-sectional study of 50 Nigerian COPD patients that respiratory HRQoL (St Georges Respiratory Questionnaire) is adversely associated with age, female sex, and dyspnoea, however the Nigerian study reported no associations with wheeze, cough, or FEV_1, probably reflecting the smaller sample size than our study[35]. The present study differs from a report from BOLD that chronic bronchitis symptoms are associated with reduced HRQoL (SF-12), and the impact is greater than for asthma or COPD[36]. In the current study, dyspnoea and wheeze symptoms were more strongly associated with HRQoL than cough and phlegm symptoms and HRQoL was adversely associated with spirometry consistent with asthma but not COPD. These differences with BOLD may be a consequence of BOLD being of cross-sectional design. Some cross-sectional studies in Africa have reported reduced HRQoL in people with asthma and after TB treatment[37–39]. In the study reported here, a previous diagnosis of TB and spirometry consistent with asthma and wheezing symptoms were adversely associated with HRQoL.

In the current study in Malawi, the differences in HRQoL independently associated with dyspnoea, wheeze, previous TB, and spirometry consistent with asthma or pure restriction exceeded the minimally important difference (MID) reported for the SF-6D instrument in longitudinal studies ((MID) (0·033, 95% CI: 0·029–0·037)) and the MIDs reported for SF-6D in people with COPD (0·011, (SD 0·09))[40].

The present study has strengths and limitations. Strengths include the use of objective validated measures of ventilatory function and HRQoL to follow-up a cohort of adults randomly identified in Malawi. Although this cohort is largely representative of adults in rural Malawi, a limitation is that nonparticipants in the original 2014 study were younger and more

likely male, anecdotally, younger men in rural villages are more likely to seek work in town/cities. The high rate of follow-up of the cohort in 2019 increases confidence in the generalizability of our findings to other similar settings. Spirometry was performed in accordance with ERS/ATS guidelines[16] and of high-quality and enabled identification of COPD independent of participant report. Limitations include biases e.g., recall, social desirability, consequent upon reliance of self-reports of symptoms, diagnoses, and exposures by participants. Further limitations include the relatively short 5-year follow-up and unavoidable use of UK tariffs embedded within SF–6D to generate HRQoL scores because appropriate and specific tariffs from relevant sub-Saharan settings have not been published. The choice of tariff does matter[41,42], and country-specific tariffs should be used where available. The study was observational and consequently we can only report associations and cannot exclude the possibility of residual confounding by factors associated with participant selection and participation.

In conclusion in this cohort study of adults living in rural Malawi the prevalence of COPD has increased by 1–2% a year and is associated with an annual rate of FEV_1 decline greater than that reported in HICs, combined with lung function deficits present before recruitment that are likely to reflect early life influences and/or sequelae of TB. Respiratory symptom burden and sub-optimal lung function are independently associated with reduced HRQoL of magnitude greater than the minimal important difference. These findings justify further research into the aetiology, natural history, and most importantly sustainable diagnosis and management of chronic respiratory diseases in sub-Saharan Africa.

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4 Unmet needs and health costs in chronic lung health – an observational population-based cohort study among adults with asthma and COPD in Malawi.

4.1 Overview

This chapter provides the estimates of health service attendance and resource use, and associated treatment cost in population cohort, as well as the additional out-of-pocket (OOP) cost per asthma or chronic obstructive pulmonary disease (COPD) patient from both health system and patient perspectives. This chapter also reports the estimated prevalence of unmet need for asthma or COPD care in Malawi both from people who accessed health facility services and those who had no health facility contact. The findings from this chapter specifically address the second objectives of my thesis of estimating the current and future economic burden of airflow obstruction from a societal perspective in Malawi. The chapter is yet to be published.

4.2 Role of the candidate

I collected additional health facility resource use and cost at a tertiary facility in Malawi, merged the collected data with health resource use data previously collected from population cohort studies in Malawi, conducted all the data analysis in this chapter, wrote the first version of the manuscript as a thesis chapter and will be the first author and corresponding author of the resultant manuscript. Revisions to the chapter were made with feedback, input, and guidance from my supervisors Graham Devereux, Louis W. Niessen, Angela Obasi and Jamie Rylance.

4.3 Abstract

4.3.1 Introduction

The underdiagnosis and undertreatment of asthma and chronic obstructive pulmonary disease (COPD) in sub-Saharan Africa is recognised but there is limited empirical economic evidence on treatment and health service coverage for these conditions. This study estimates the health costs and unmet need of COPD and asthma case management in Malawi.

4.3.2 Methods

This economic study takes health provider and patient perspectives. Patient health resource use and costs were obtained from three cohort studies in southern Malawi. Health provider input and costs were obtained from one of these studies and a bespoke costing study at a chest clinic at Queen Elizabeth Central Hospital (QECH).

The three cohort studies were a rural Chikwawa lung health cohort of 1481 adults recruited in 2014, an urban Blantyre cohort of 405 adults with pulmonary tuberculosis recruited in 2016 and a cohort of 805 adults admitted in QECH recruited in 2014 all of which represented the catchment area for QECH. We identified the participants with asthma (wheeze in last year) and COPD (atypical lung function) from the three cohorts and pooled them to get a dataset from which we could estimate an annual total per patient cost of asthma and COPD.

Annual per capita costs of asthma and COPD were estimated. An ingredient approach was used to estimate resource use and costs and reported in 2020 US$ while adjusting for inflation with a one-year time horizon. We conducted a non-parametric bootstrap analysis to assess the uncertainties around the mean total annual per patient asthma and COPD costs and their respective reported 95% confidence intervals.

4.3.3 Results

Of 1493 Malawian adults, 226 accessed health facilities in the previous year. 11.9% (n=27) had asthma, of these 26% (n=7) used regular medication and 22% (n=6) had an inpatient admission in the previous year. 9.7% (n=22) had COPD, 23% (n=5) of whom used regular medication and 13.6% (n=3) had an inpatient admission in the previous year. Guideline defined needs for 74.1% of those with asthma and 77.3% of those with COPD were unmet. Annual cost for an asthma patient is US$ 108.25 (95% CI: 86.68–131.75) and for COPD US$ 143.39(95% CI: 123.61–165.11), most of these costs being for hospital treatment of exacerbation. For those with no health facility contact (72 asthma, 247 COPD), 95.8% of those with asthma and 97.2% of those with COPD had an unmet guideline defined need.

4.3.4 Conclusion

The estimated costs of asthma and COPD in Malawi are substantial and exceed Malawi's average annual per-capita health expenditure (US$35) and there are substantial unmet needs. These findings justify efforts to mobilise resources for under resourced health systems and research into identifying sustainable, optimal and equitable diagnosis and management strategies for Chronic respiratory diseases (CRDs) in Africa.

4.4 Introduction

Chronic obstructive pulmonary disease (COPD) and asthma are the most prevalent chronic respiratory diseases (CRDs)[1] with COPD accounting for an estimated 6% of all deaths worldwide[2,3] of which 90% are in populations living in low and middle income (LMIC) settings[4]. About 358 million people are affected by asthma and 174 million people are affected by COPD[3,5]. It is well-recognised and recommended that incurable CRDs such as asthma and COPD need long term treatment and clinical follow-up. Knowing the true respiratory disease burden in LMICs coupled with the unit costs of cost-effective interventions has potentially profound implications for the prioritisation and provision of respiratory health services and the design of crucial CRD care and programmes.

Although several population based surveys have reported a high prevalence of respiratory symptoms[6–8], obstructive and restrictive (low lung volumes) lung function[8–14] in LMICs, few studies have reported and described the economic and health burden of chronic respiratory diseases in LMICs[15]. In high income settings, studies have reported annual direct medical cost for asthma care ranging from US$150/year in Abu Dhabi to more than US$3000/year in United States whilst the direct medical costs of COPD have ranged from US$670/year in Denmark to more than US$4500/year in United States[16]. In LMICs, given the scarcity of resources and intense competition from interventions seeking priority, there is a pressing need to better document the unit cost of CRD interventions. This evidence can be used by policymakers in the planning and budgeting of selective interventions and to mobilize resources for scale-up of cost-effective interventions within the Malawian health system.

We therefore set out to estimate the unmet need and health costs for CRD care in the Malawian health system, in particular for COPD and asthma case management. We measured

health service attendance and resource use, and associated treatment cost in population cohorts, as well as the additional out-of-pocket (OOP) cost per patient.

4.5 Study setting and methodology

4.5.1 Study site setting

Malawi is a landlocked south-eastern African country with 83% of its 18 million inhabitants living in rural areas[17]. With a GDP per capita of $300, it is one the poorest countries in the world[18]. Over half the households live below the poverty line[19]. Blantyre is the country's centre of finance and commerce and the country's second largest city and the capital of the Southern region of the country. Chikwawa is a district in the southern region of Malawi where we have established the Chikwawa lung health cohort to investigate the life course of airways disease[6].

Health care in Malawi is provided through public, private for profit and private not for profit health facilities[20]. 48% of the facilities are government owned (public health facilities), 22% are owned by non-governmental organisations of which the Christian Health Association of Malawi is the largest, 30% are owned by private individuals and companies and run for profit[20]. About 50% of the Malawian national health expenditure is funded from external donors[21,22].

4.5.2 Study design and participants.

We estimated costs data from health provider and patient (household) perspectives. We used data from the community based Chikwawa lung health described in chapter two of this thesis and two additional adult cohorts: an urban and a health facility cohort, with participants with COPD or asthma. Due to the low number of participants who used health facilities and systems from the Chikwawa lung health cohort and to improve the generalizability of our health service attendance and resource use, and associated treatment cost estimates[23], we pooled the individual participant data with cohort studies that had a similar study design, were from a comparable geographic region, and collected the lung function and health

resource use data with broadly similar tools and questionnaires. The data from the three observational cohort studies of adults from which we pooled data to estimate the patient and household perspective costs were conducted in southern Malawi.

The studies we used to estimate the patient and household perspective costs were; i) the pulmonary tuberculosis (TB) urban cohort, ii) the Chikwawa lung health rural cohort, and iii) the Queen Elizabeth Central hospital (QECH) admission cohort; all these cohort studies represented the catchment area for QECH, the largest tertiary health facility in southern Malawi. We accessed individual level data from a total of 1886 participants from; the Chikwawa lung health cohort (n=1481) and the pulmonary TB cohort (n=405). In brief, the participants in the Chikwawa lung health cohort were a randomized age, sex-stratified sample of adults living in Chikwawa while in the pulmonary TB cohort the inclusion criteria were; age ≥ 15years, residence in urban Blantyre, treatment for a first episode of pulmonary tuberculosis (TB) with cure or completion as defined by the Malawi National Treatment Programme [12]. In both these studies, the participant's lung function (forced expiratory volume in one second [FEV_1] and forced vital capacity [FVC]) was measured using the ndd EasyOne Spirometer (ndd Medizintechnik AG, Zurich, Switzerland), before and 15 minutes after administration of inhaled salbutamol (200 μg) administered via spacer device. To be included in this costing analysis, participants had to have on record acceptable spirometry based on the American Thoracic Society (ATS) and European Respiratory Society (ERS) acceptability and reproducibility criteria[24]. 20.8% (n=393) participants were excluded for lacking an acceptable spirometry reading from the combined dataset from the Pulmonary TB and Chikwawa lung health cohorts. Figure 4-1 outlines the participants with their various lung functions or chronic respiratory disease characteristic from the patients from whom we were able to access individual level data. We only accessed aggregate data from the QECH hospital cohort. The

QECH hospital cohort systematically recruited every fifth adult admission from the ward registers at QECH.

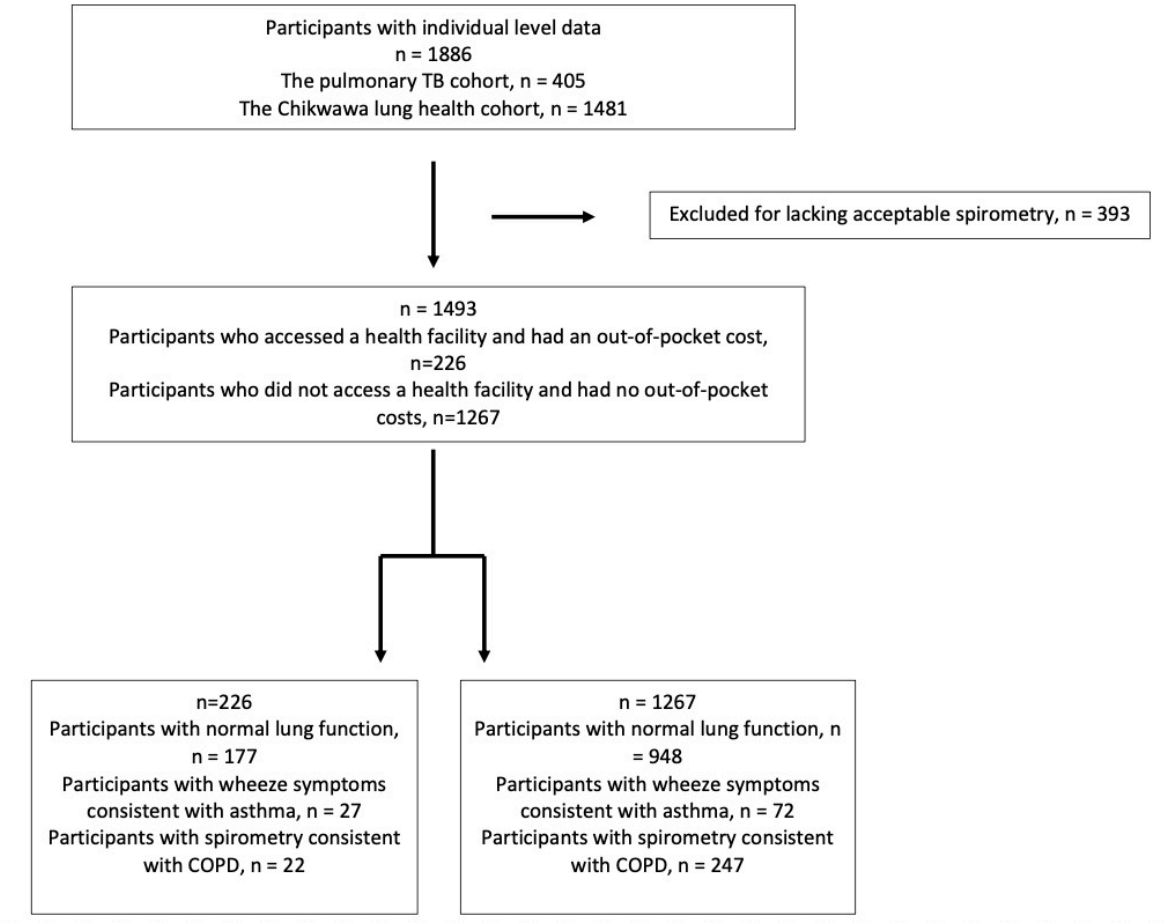

Figure 4-1: Number of participants in the study from whom we obtained individual level data.

The health provider costs were estimated from a costing study conducted at the chest clinic at QECH, and the QECH admission cohort mentioned above. A brief description of the details to the studies we used and the data that was collected in each study is provided in the costing methods section below.

4.5.3 Costing methods

Patient costs

For patient costs we analysed primary data from three cohort studies to obtain estimates of the health resource use and out-of-pocket costs for CRD care. The three cohort studies have been described elsewhere[6,12,25], in brief the:

i. The pulmonary TB cohort comprised 405 adults with pulmonary tuberculosis (a risk factor for COPD[26]) expected to complete treatment who were prospectively identified and recruited in February 2016 and followed up until April 2018. These study participants attended the Queen Elizabeth Central Hospital (QECH) to obtain health care[12]. This cohort provided the following individual patient related cost and lung function data: exacerbation frequency, out-of-pocket outpatient care costs (non-TB Clinic fees, non-TB drug costs including antibiotics, travel, food, and airtime), out-of-pocket admission costs (admission fees and tests, drug costs including antibiotics, travel, food, and airtime), pre and post-bronchodilator forced expiratory volume at 1 second (FEV_1), forced vital capacity (FVC).

ii. QECH admission cohort 805 adult participants (every fifth adult patient) admitted to QECH and followed up between June and December 2014 to provide their aggregate medical diagnoses and resource use data per patient discharge medical diagnosis. In addition to patient data this study also estimated health provider costs by undertaking a resource-based costing study[25].

iii. The Chikwakwa lung health cohort of 1481 adults was a general population sample, randomly selected and followed up between 2014 and 2020 to provide rates of change of lung function, diagnosed lung disease, associated health resource use and costs arising from using the health system due to atypical lung function[6]. This cohort provided the following individual patient related cost and lung function data: hospital diagnosed lung diseases (including asthma and COPD), out-of-pocket outpatient care

costs (Clinic fees, drug costs including antibiotics, travel, food, and airtime), out-of-pocket admission costs (admission fees and tests, drug costs including antibiotics, travel, food, and airtime), pre- and post-bronchodilator FEV_1 and FVC.

In all the cohort studies, questionnaires administered in Chichewa were used to collect the health resource use and cost data while lung function measurement was obtained from spirometry.

Health provider costs

iv. Alongside the Chikwakwa lung health cohort, fourth study: we carried out a detailed micro-costing study to supplement the cohort data on resources by diagnosis from the previous studies[6,25], we also undertook a costing study at the chest clinic of QECH to collect data on staffing and time spent reviewing patients with respiratory diseases[6]. The chest clinic at QECH is the regional free-to-access specialist outpatient clinic for all patients with respiratory complaints. All the patients at QECH shared clinical staff, pharmacy, and outpatient services.

4.5.4 Current clinical care and lung health guidelines

Presently, the Malawian health system recommends the adoption of the essential medication guidelines recommended by the WHO[27]. These recommend the use of oral or inhaled short-acting beta-agonists (SABA) such as salbutamol to relieve symptoms of asthma and inhaled corticosteroids (ICS) such as beclomethasone for moderate/severe asthma to improve lung function, reduce asthma mortality and frequency and severity of exacerbations[27]. For COPD, SABA are recommended to relieve breathlessness while to improve lung function in the short term, ICS are recommended for $FEV_1 < 50\%$ predicted[27]. Long-acting bronchodilators are recommended for patients with COPD who remain symptomatic despite SABA treatment[27]. In a recently completed Malawi health service provision assessment survey[28], the available

essential medicines, commodities and equipment for asthma and COPD in Malawian health facilities were: salbutamol inhalers/tablets (93%), injectable epinephrine (64%), prednisolone tablets (43%), hydrocortisone injection (22%), oxygen (16%), beclomethasone inhalers (6%), peak flow meters (2%), and spacers for inhalers (9%)[28]. Three-quarters of the facilities provide support services for diagnosis, prescription or management of patients with CRD but only 12% of staff are trained in the provision of CRD service[28]. Patients frequently present at health facilities during episodes of acute exacerbation, receive outpatient care and later discharged to their homes. In contrast to high income countries, outpatient care in Malawi is the unscheduled emergency care received by the patients with acute/sub-acute exacerbation of respiratory symptoms at health facilities. Scheduled 'out-patient' care at health facilities in the first instance is not the norm in Malawi. Only patients with severe respiratory symptoms are admitted for inpatient care.

We costed the CRD care for clinical conditions as defined through symptoms or spirometry[29] and identified as leading the CRD morbidity and mortality in Malawi by the Ministry of Health[30].

The following operational definitions were used for asthma and COPD:

For COPD we used the Global Initiative for Chronic Obstructive lung disease (GOLD) recommendation of FEV1/FVC < 70%[31,32] with mild COPD being defined as $FEV_1 \geq 80\%$ predicted and moderate/severe COPD being defined as $FEV_1 < 80\%$ predicted with or without exacerbation leading to outpatient care or admission[31,32].

For asthma, the two definitions commonly used in epidemiological studies were used; 'Doctor diagnosed asthma' comprised all those who reported a doctor diagnosis of asthma, and current asthma comprised those who reported the symptom of wheeze in the last 12 months[33,34]. Mild asthma was defined as those with asthma with no exacerbations in the

previous year while moderate/severe asthma was defined as one or more exacerbation in the previous year leading to outpatient care or admission.

The clinical conditions are:

- Patients with mild COPD.
- Patients with moderate/severe COPD.
- Patients with mild asthma.
- Patients with moderate/severe asthma.

4.5.5 Collection of cost data and measuring resource use

All the studies used structured questionnaires to collect information.

Patient costs

The pulmonary TB cohort, QECH hospital admission cohort and Chikwakwa lung health cohort collected patient related data; demographic characteristics, participant/patient travel costs, cost of food, airtime expenses, out-of-pocket expenses incurred by out-patient visits and admissions, and days-off work and participant incomes to estimate productivity losses incurred through the use of questionnaires administered in Chichewa. The reference case unit cost for productivity loss from absence from work was estimated as the minimum wage in Malawi in 2019[35].

Health facility costs

The QECH hospital admission cohort and Chikwakwa lung health cohort micro-costing study collected data on the number and level of health staff to estimate salary and related staff cost, medication and consumables, admission expenses, medical equipment such as sphygmomanometers, furniture, and rental space. This was through the administration of questionnaires.

Other costs

Some out-patient medications for severe asthma and COPD such as beclomethasone inhalers were not easily available in Malawi[27]. We estimated their cost/treatment as recommended by the Malawian Ministry of Health[27,28] by extracting their unit cost from an accessible international price guide[36] and assuming adherence by the patient if the medication was available.

4.5.6 Statistical analysis, costing approach, time horizon and price adjustments.

We used one year as our time horizon. We estimated the cost of CRD patient case management per year by summing the cost of all patient episodes of care in a year from both the health provider and patient perspectives so that we could include out-of-pocket payments and productivity losses. We used an ingredient approach to resource use and costing[37] and followed consolidated health economic evaluation reporting standards (CHEERS) guidelines[38]. This entails the identification of relevant inputs that are used to deliver CRD care, their quantities, and their monetary value.

We calculated total annual health provider cost, and from the patient perspective, out-of-pocket participant cost and productivity losses by clinical condition. We assigned costs related to medicine, staff salaries, out-of-pocket expenses, and productivity losses. Direct health provider costs per patient visit were estimated from total annual provider cost of the chest clinic divided by the number of patient visits. The total societal cost per patient was estimated by summing the direct health provider cost, patient the out-of-pocket costs and the productivity losses. As the health utilization and cost data were skewed, we conducted a non-parametric bootstrap analysis of 100,000 resamples with replacement of the original reported participant data[39] to assess the uncertainties around the mean total annual health outcomes and mean total annual per patient asthma and COPD costs and their respective reported 95% confidence intervals (95% CI).

We estimated proportion of unmet need for healthcare and the total cost of addressing this need in this cohort. Unmet need for healthcare was defined as the need for access to adequate healthcare by either; a) patients with untreated disease as those who did not access a health facility while having wheeze symptoms consistent with asthma or spirometry consistent with COPD or, b) patients with suboptimal access to asthma/COPD care as those who accessed a health facility but did not receive long term respiratory medication or healthcare[40].

We adjusted for inflation using the GDP deflator[41,42] for Malawi obtained from the World Bank[43] to adjust all cost to 2020 base year and used an exchange rate of 1 US$ = 749.527 Malawian Kwacha (MWK)[44]. The exchange rate we used to convert MWK to US$ was derived from the World Bank and accessed on 12 May 2021[44]. We report our finding in 2020 MWK and US$ and their respective interquartile ranges (IQR) or 95% UI. All analysis was conducted using R v3·6·0 and MS Excel.

4.5.7 Ethical approval

The study protocol was approved by the Liverpool School of Tropical Medicine Research Ethics Committee (19-005) and the Malawi College of Medicine Research and Ethics Committee (COMREC, P.03/19/2617). Written informed consent was obtained from all participants.

4.6 Results

4.6.1 Demographic characteristics

Table 4-1 presents the demographic characteristics of those in the pulmonary TB cohort and the Chikwakwa lung health cohort who had acceptable spirometry (Pulmonary TB cohort, N = 405 (27%) participants and Chikwakwa lung health cohort, N= 1088 (73%) participants). Mean (SD) participant age was 45 (16) years, 758 (51%) were men and on average participants had completed 5.4 (4.6) years of education. The summary statistics of the demographic characteristics from the QECH hospital admission cohort are presented in a previous publication [25], in brief; from the 647 who had a complete dataset, the majority were male (53.0%, n=343), had completed 8 years of basic education (55.8%, n=361) and were aged between 25–44 years (57.0%, n=369). There were differences in the demographic characteristics of participants in the pulmonary TB cohort compared to the Chikwakwa lung health cohort. Chikwakwa lung health cohort's participants were older, the majority were female (56%, n/N = 605/1088), had fewer years of education and a majority did not incur an out-of-pocket healthcare cost.

Table 4-1: Demographic characteristics of cohort study participants from whom we obtained individual level data.

Characteristics	Total sample size, n = 1493[Ø]	The Pulmonary TB cohort, n = 405[Ø]	The Chikwawa lung health cohort, n = 1088[Ø]	P value[#]
Health resource use				<0.001
Incurred an out-of-pocket cost	15% (226/1493)	47% (192/405)	3.1% (34/1088)	
Did not incur an out-of-pocket cost	85% (1267/1493)	53% (213/405)	97% (1054/1088)	
Sex; Male	51% (758/1493)	68% (275/405)	44% (483/1088)	<0.001
Age (years)	45 (16)	35 (10)	49 (16)	<0.001
Grouped age (years)				<0.001
<30	17% (259/1493)	31% (127/405)	12% (132/1088)	

30 – 39	28% (411/1493)	43% (176/405)	22% (235/1088)	
40 – 49	22% (327/1493)	20% (81/405)	23% (246/1088)	
50 – 59	14% (212/1493)	2.7% (11/405)	18% (201/1088)	
60 – 69	9.5% (142/1493)	1.5% (6/405)	12% (136/1088)	
70 – 79	6.1% (91/1493)	0.7% (3/405)	8.1% (88/1088)	
>=80	3.4% (51/1493)	0.2% (1/405)	4.6% (50/1088)	
Years of schooling completed	5.4 (4.6)	9.4 (3.6)	3.9 (4.0)	<0.001
BMI (kg/m^2)	21.5 (3.7)	20.8 (2.9)	21.7 (3.9)	0.001
BMI,				<0.001
Underweight (< 18.5)	16% (246/1493)	18% (71/405)	16% (175/1088)	
Normal weight (≥18.5; <25.0)	70% (1036/1493))	75% (304/405)	67% (734/1088)	
Overweight (≥25.0; <30.0)	10% (155/1493)	6.2% (25/405)	12% (130/1088)	
Obese (≥ 30.0)	3.6% (54/1493)	1.2% (8/405)	4.5% (49/1088)	

[Ø] % (n/N); Mean (SD)

[#] Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test.

Comparison of the pooled demographic and health characteristics of those participants who incurred out-of-pocket hospital costs to those who did not and from whom we obtained individual level data (Table *4-2*, Table 4-3 & Table 4-4) indicated that those who incurred costs were younger (mean difference [MD] (95% CI): 6.9 years (5.0, 8.7)), more educated (MD: 3.9 years, 3.3, 4.5), more male (percentage difference[PD] (95% CI): 11.6% (4.4, 18.8%)), had reduced FEV_1 %predicted (MD: 3.4%, 0.8, 5.9) and FVC %predicted (MD: 6%, 3.6, 8.5), were more likely to have wheeze symptoms consistent with asthma (PD: 6.2%, 1.6, 10.9), less likely to have spirometry consistent with COPD (PD: 9.8%, 5.1, 14.5) and more likely to report cough, shortness of breath and phlegm symptoms. There was no significant difference in the percentage of people diagnosed with either asthma or COPD and the BMI between the two groups of participants.

Table 4-2: Characteristics of study participants who used health facilities and incurred out-of-pocket hospital costs from the Pulmonary TB and Chikwakwa lung health cohorts.

Characteristics	Total (The pulmonary TB and Chikwawa lung health cohorts), n=226[Ø]	The Pulmonary TB cohort, n=192[Ø]	The Chikwawa lung health cohort, n=34[Ø]	P value[#]
Sex; Male	61% (137/226)	66% (126/192)	32% (11/34)	<0.001
Age (years)	40 (12)	37 (10)	52 (15)	<0.001
Grouped age (years)				<0.001
<30	19% (43/226)	22% (42/192)	2.9% (1/34)	
30 – 39	41% (92/226)	45% (86/192)	18% (6/34)	
40 – 49	26% (59/226)	25% (48/192)	32% (11/34)	
50 – 59	6.6% (15/226)	4.7% (9/192)	18% (6/34)	
60 – 69	4.0% (9/226)	2.1% (4/192)	15% (5/34)	
70 – 79	3.1% (7/226)	1.6% (3/192)	12% (4/34)	
80 – 89	0.4% (1/226)	0% (0/192)	2.9% (1/34)	
Years of schooling completed	8.7 (4.2)	9.4 (3.7%)	4.8 (4.4)	<0.001
BMI (kg/m^2)	21.5 (3.9)	21.2 (3.3)	22.9 (6.4)	0.6
BMI,				<0.001
Underweight (< 18.5)	18% (41/226)	17% (32/192)	26% (9/34)	
Normal weight (≥18.5; <25.0)	67% (151/226)	72% (138/192)	38% (13/34)	
Overweight (≥25.0; <30.0)	12% (26/226)	9.4% (18/192)	24% (8/34)	
Obese (≥ 30.0)	3.5% (8/226)	2.1% (4/192)	12% (4/34)	

[Ø] % (n/N); Mean (SD)

[#] Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test.

Table 4-3: Demographic characteristics of cohort study participants from whom we obtained individual level data.

Characteristics	Total sample size, n = 1493[Ø]	Incurred out-of-pocket healthcare costs, n = 226[Ø]	Did not incur out of pocket healthcare costs, n = 1267[Ø]	P value[#]
Study				<0.001
Pulmonary TB cohort	27% (405/1493)	85% (192/226)	17% (213/1267)	
Chikwawa lung health cohort	73% (1088/1493)	15% (34/226)	83% (1054/1267)	
Sex; Male	51% (758/1493)	61% (137/226)	49% (621/1267)	0.001

Age (years)	45 (16)	40 (12)	46 (17)	<0.001
Grouped age (years)				<0.001
<30	17% (259/1493)	19% (43/226)	17% (216/1267)	
30 – 39	28% (411/1493)	41% (92/226)	25% (319/1267)	
40 – 49	22% (327/1493)	26% (59/226)	21% (268/1267)	
50 – 59	14% (212/1493)	6.6% (15/226)	16% (197/1267)	
60 – 69	9.5% (142/1493)	4.0% (9/226)	10% (133/1267)	
70 – 79	6.1% (91/1493)	3.1% (7/226)	6.6% (84/1267)	
>=80	3.4% (51/1493)	0.4% (1/226)	3.9% (50/1267)	
Years of schooling completed	5.4 (4.6)	8.7 (4.2)	4.8 (4.4)	<0.001
BMI (kg/m^2)	21.5 (3.7)	21.5 (3.9)	21.5 (3.6)	>0.9
BMI,				0.8
Underweight (< 18.5)	16% (246/1493)	18% (41/226)	16% (205/1267)	
Normal weight (≥18.5; <25.0)	70% (1036/1493))	67% (151/226)	70% (887/1267)	
Overweight (≥25.0; <30.0)	10% (155/1493)	12% (26/226)	10% (129/1267)	
Obese (≥ 30.0)	3.6% (54/1493)	3.5% (8/226)	3.6% (46/1267)	

[Ø] % (n/N); Mean (SD)

[#] Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test.

Table 4-4: Clinical and respiratory characteristics of study participants from whom we obtained individual level data.

Characteristics	**Total sample size, n = 1493[Ø]**	**Incurred out-of-pocket healthcare costs, n = 226[Ø]**	**Did not incur out of pocket healthcare costs, n = 1267[Ø]**	**P value[#]**
Spirometry				
FEV_1, %predicted	90% (20)	87% (18)	91% (20)	0.010
FVC, %predicted	96% (20)	91% (17)	97% (20)	<0.001
FEV_1/FVC	77% (11)	80% (10)	77% (11)	<0.001
Clinical characteristics				
Asthma				<0.001
No asthma	93% (1394/1493)	88% (199/226)	94% (1195/1267)	
Mild asthma	5.0% (74/1493)	4.0% (9/226)	5.1% (65/1267)	
Moderate/Severe asthma	1.7% (25/1493)	8.0% (18/226)	0.6% (7/1267)	
Doctor diagnosed asthma	1.9% (29/1493)	3.1% (7/226)	1.7% (22/1267)	0.270
COPD				0.001
No COPD	82% (1224/1493)	90% (204/226)	81% (1020/1267)	
Mild COPD	7.8% (116/1493)	3.1% (7/226)	8.6% (109/1267)	

Moderate/Severe COPD	10% (153/1493)	6.6% (15/226)	11% (138/1267)	
Doctor diagnosed COPD	0.1% (1/1493)	0	(1/1267)	
Respiratory symptoms				
Cough most days of the month for ≥3 months of the year	27% (405/1493)	36% (81/226)	26% (324/1267)	0.001
Shortness of breath when hurrying on the level or walking up a slight hill	16% (237/1493)	41% (92/226)	11% (145/1267)	<0.001
Usually brings up phlegm from chest	14% (215/1493)	28% (64/226)	12% (151/1267)	<0.001

[Ø] % (n/N); Mean (SD)

[#] Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test.

4.6.2 Respiratory Symptoms

Table 4-5 presents clinical and respiratory symptoms of participants in the Pulmonary TB cohort and the Chikwawa lung health cohort who incurred an out-of-pocket healthcare cost. In the total sample of 226 participants, cough was reported by 36% (n=81), shortness of breath when hurrying on the level or walking up a slight hill by 41% (n=92) and chronic sputum expectoration was reported by 28% (n=64). Based on wheeze symptoms, 12% (n=27) fulfilled the definition of current asthma and 9.8% (n=22) had spirometry consistent with COPD. Only 7 participants (25.9% of those with wheeze symptoms) reported an established doctor diagnosis of asthma while no participant reported an established COPD diagnosis made by a doctor. There was no significant difference in the respiratory symptoms reported except for shortness of breath when hurrying on the level or walking up a slight hill (p=0.03).

Table 4-5: Clinical and respiratory characteristics of study participants who incurred out-of-pocket hospital costs from the Pulmonary TB and Chikwawa lung health cohorts

Characteristics	Total, n=226[Ø]	The Pulmonary TB cohort, n=192[Ø]	The Chikwawa lung health cohort, n=34[Ø]	P value[#]
Spirometry				
FEV_1, %predicted	87% (18)	88% (18)	84% (16)	0.15
FVC, %predicted	91% (17)	90% (16)	94% (22)	0.8
FEV_1/FVC	80% (10)	81% (10)	74% (13)	<0.001
Clinical characteristics				
Asthma				0.002
No asthma	88% (199/226)	90% (173/192)	76% (23/34)	
Mild asthma	4% (9/226)	4.7% (9/192)	0% (0/34)	
Moderate/Severe asthma	8% (18/226)	5.2% (10/192)	24% (8/34)	
Doctor diagnosed asthma	3.1% (7/226)	2.6% (5/192)	5.9% (2/34)	0.631
COPD				0.047
No COPD	90% (203/225)	92% (176/191)	79% (27/34)	
Mild COPD	3.1% (7/225)	2.6% (5/191)	5.9% (2/34)	
Moderate/Severe COPD	6.7% (15/225)	5.2% (10/191)	15% (5/34)	
Doctor diagnosed COPD	0.0% (0/225)			
Respiratory symptoms				
Cough most days of the month for ≥3 months of the year	36% (81/226)	34% (65/192)	47% (16/34)	0.14
Shortness of breath when hurrying on the level or walking up a slight hill	41% (92/226)	44% (84/192)	24% (8/34)	0.027
Usually brings up phlegm from chest	28% (64/226)	27% (51/192)	38% (13/34)	0.2

[Ø] % (n/N); Mean (SD)

[#] Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test.

4.6.3 Health service resource use

Table 4-6 describes the health resource use of the participants with wheeze symptoms consistent with asthma or spirometry consistent with COPD. A minority of participants used regular medication at home, 26% (n=7) of those with asthma and 23% (n=5) of those with

COPD, 28% (n=5) of patients with moderate/severe asthma and 33% (n=5) of patients with moderate/severe COPD used medication for their lung complaint. 35 participants (15% of the total sample) were found to have reported an exacerbation event. In those participants with a reported exacerbation, the median number of reported exacerbations was 3 exacerbations (IQR 1–4). 28% (n=5) and 13% (n=2) of those with moderate/severe asthma and moderate/severe COPD respectively required in-patient admission after a reported exacerbation event. For those with wheeze symptoms consistent with asthma, mean number of exacerbations per year was 1.14 (SD:1.09), with those with mild asthma being 0.00 (SD: 0.00), and those with moderate/severe asthma being 1.72 (SD: 0.89). For those with spirometry consistent with COPD, mean number of exacerbations per year was 1.36 (SD: 1.18), with those with mild COPD being 0.86 (SD: 1.07), and those with moderate/severe COPD being 1.60 (SD: 1.18). 18.4% (n= 9 out of 49 participants with asthma or COPD) used inpatient admission services. Of the participants with asthma, 22.2% (n= 6 out of 27) had been admitted while 13.6% (n= 3 out of 22) of participants with COPD had been admitted.

Table 4-6: Health service utilisation by study participants with asthma or COPD from the Pulmonary TB and Chikwawa lung health cohort.

Health service use and utilisation	**Mild asthma, n=9[Ø]**	**Moderate/Severe asthma, n=18[Ø]**	**Mild COPD, n=7[Ø]**	**Moderate/Severe COPD, n=15[Ø]**
Use medication	22% (2/9)	28% (5/18)	0% (0/7)	33% (5/15)
Total annual number of outpatient visits				
1 outpatient visit	67% (6/9)	50% (9/18)	71% (5/7)	47% (7/15)
> 1 outpatient visit	33% (3/9)	50% (9/18)	29% (2/7)	53% (8/15)
Mean Outpatient visits per year (SD)	1.89 (1.54)	2.00 (1.37)	1.57(1.13)	1.73(0.80)
Total annual number of inpatient visits				
Had ≥ 1 Inpatient admission in the past year	11% (1/9)	28% (5/18)	14% (1/7)	13% (2/15)
Mean inpatient admission in the past year (SD)	0.11 (0.33)	0.28(0.57)	0.14(0.38)	0.13(0.35)
Had a self-reported exacerbation in the past year.	0% (0/9)	100% (18/18)	57% (4/7)	87% (13/15)
Mean self-reported exacerbation in the past year (SD)	0 (0)	1.72 (0.89)	0.86 (1.07)	1.60 (1.18)
Productivity losses				
Mean days lost from work in the past year (SD)	7 (13)	4 (10)	1 (3)	7 (12)

[Ø] % (n/N); Mean (SD)

4.6.4 Unit prices for the resources and medicine dosage per asthma or COPD severity and assumptions used in the costing

Table 4-7 highlights the ingredient unit costs that were extracted and used to estimate the cost of care of care for participants with asthma or COPD at QECH. Table 4-8 and Table 4-9 report the medication used for asthma and COPD care at QECH and their recommended dosages and treatment durations while Table 4-10 reports the assumptions that have been used to estimate the costs estimated. The medicines for which we report the unit cost were: salbutamol (SABA), aminophylline, beclomethasone (ICS), prednisolone, hydrocortisone and two antibiotics on the WHO essential medication list[36,45].

Table 4-7: Ingredient input prices unit costs in 2020.

Item	Unit of measure	Item unit cost		Source
		MWK	USD	
Patient unit costs				
Medicines				[34]
Salbutamol	Inhaler, 100mcg/dose, 200 doses/inhaler	6.88[&]	0.01	[34]
Aminophylline	Tablet, 100 mg	104.38	0.14	
Steroids/Corticosteroids				
Beclomethasone	Inhaler, 100mcg/dose, 200 doses/inhaler	13.28[&]	0.02	
Prednisolone	Tablet; 5 mg	43.17	0.06	
Hydrocortisone	Injection; 100mg	616.78	0.82	
Antibiotics				
Bactrim (co-trimoxazole)	Tablet; 960 mg	37.24	0.05	
Amoxicillin	Tablet 500 mg	45.19	0.06	
Productivity losses				
Lost income	Minimum government mandated daily wage	1923.08	2.57	[33,44]
Health facility costs				

Building	Annualised cost of a room of dimensions 3*3 metres	23,690.33	31.61	[23]
Admission costs	Per day admission costs	8481.07	11.32	[23]
Staff costs				[6,23]
Clinical Manager	Monthly salary	357,065.00	476.39	
Nursing officer	Monthly salary	257,665.17	343.77	
Ward Clerk	Monthly salary	99,879.00	133.26	
Research Assistant	Monthly salary	199,980.00	266.81	
Data entry Clerk	Monthly salary	99,879.00	133.26	
Cleaner	Monthly salary	97,626.00	130.25	
Patient attendant	Monthly salary	99,879.00	133.26	
Medical equipment cost				[6,23]
Sphygmomanometer	Digital Blood pressure machine/cuff; Annualised cost	24,621.84	32.85	
Stethoscope	Standard chest piece; Annualised cost	43,445.47	57.96	
Weighing scale	Digital; Annualised cost	7,497.41	10.00	
Digital thermometer	Digital; Annualised cost	1,390.57	1.86	
Nebulizer Machine	Annualized cost of use.	794,910.00	1,060.55	
Diagnosis				[6]
Spirometer	Portable spirometer; Annualised cost of use.	35,409.70	47.24	
Inhaler spacer	Plastic, for spirometry	658.00	0.88	
Spirette	Disposable plastic mouthpiece	329.00	0.44	
Nose clip	Plastic, for spirometry	110.00	0.15	
Furnishings				[6,23]
Benches	Annualized cost of use	101,461.10	135.37	
Patient couch	Annualized cost of use	188,353.09	251.30	
Trolley	Annualized cost of use	976,285.69	1,302.54	
Desks	Annualized cost of use	255,392.15	340.74	
Table	Annualized cost of use	112,261.85	149.78	
Chairs	Annualized cost of use	261,932.09	349.46	

	Benches	Annualized cost of use		101,461.10	135.37

[&] This is the cost per dose (cost per puff). A unit of inhaler has 200 doses (puffs).

Table 4-8: Medicines available for asthma and COPD at Queen Elizabeth Central Hospital (QECH).

Medicine	Mild symptomatic asthma	Severe/Moderate Asthma	Mild COPD	Severe/Moderate COPD	Exacerbation Asthma/COPD	Source of information for type of medicine used
Bronchodilators						Primary data collection from the chest clinic at QECH and consultation with respiratory health clinicians.
Salbutamol	X	X	X	X	x	
Aminophylline		X		X	x	
Steroids/Corticosteroids*						Primary data collection from the chest clinic at QECH and consultation with respiratory health clinicians
Beclomethasone		X		X		
Prednisolone		X		X	x	
Hydrocortisone		X		X	x	
Antibiotics#						Primary data collection from the chest clinic at QECH and consultation with respiratory health clinicians
Bactrim	X	X	X	X		
Amoxicillin	X	X	X	X	x	

*The steroids/corticosteroids are provided alternatively to the patient on an as needed basis.
#In some cases, physicians prescribe a dose of antibiotics to alleviate chest infections to people who have chest infection symptoms of chest infections such as coughing and breathlessness.

Table 4-9: Minimal medicines, dosages, and treatments to control asthma and COPD.

Medicine	Formulation	Dose	Source of information for type of medicine used
Patients with mild asthma			
Salbutamol	Tablet	4 mg 3 – 4 times a day, maximum single dose 8 mg. Inhalation route preferred.	[25,26]
Salbutamol	Inhaler. Preferred option.	100 mcg contained in one inhaler has 200 doses. 1 puff a day to account for non-adherence	[25,26,45]
Bactrim (co-trimoxazole)	Tablet	960 mg twice daily for 5 days	[23,25]
Amoxicillin	Tablet	500 mg 3 times a day for 5 days.	[23,25]
Patients with severe/Moderate Asthma			
Salbutamol	Inhaler	200 puffs from one inhaler. 2 puffs a day every day.	[25,26,45]
Aminophylline	Tablet	200mg twice a day for 1 week reduced to 100mg twice a day to factor in non-adherence.	[23,25]
Beclomethasone	Inhaler	50 – 200 µg twice daily; 200 puffs from one inhaler. 2 puffs twice a day or 1 to account for non-adherence	[25]
Prednisolone	Tablet	30 mg daily for at least 7 days	[23,25,45]
Hydrocortisone	Intravenous Injection	200mg, administered after usual dose of Prednisolone or Beclomethasone.	[23,25,45]

Bactrim (co-trimoxazole)	Tablet	960 mg twice daily for 7 days	[23,25]
Amoxicillin	Tablet	500 mg 3 times a day for 7 days.	[23,25]
Patients with mild COPD			
Salbutamol	Tablet	4 mg 3 – 4 times a day, maximum single dose 8 mg. Inhalation route preferred.	[25,26]
Salbutamol	Inhaler. Preferred option	100 mcg contained in one inhaler has 200 doses. 1 puff a day to account for non-adherence	[25,26,45]
Bactrim (co-trimoxazole)	Tablet	960 mg twice daily for 5 days	[23,25]
Amoxicillin	Tablet	500 mg 3 times a day for 5 days.	[23,25]
Patients with severe/Moderate COPD			
Salbutamol	Inhaler	200 puffs from one inhaler. 2 puffs a day every day.	[25,26,45]
Aminophylline	Tablet	200mg twice a day for 1 week reduced to 100mg twice a day to factor in non-adherence.	[23,25]
Beclomethasone	Inhaler	50 – 200 µg twice daily. 200 puffs from one inhaler. 2 puffs twice a day or 1 to account for non-adherence.	[25]
Prednisolone	Tablet	30 mg daily for 7 days if increased breathlessness interferes with daily activities.	[23,25,45]
Hydrocortisone	Intravenous Injection	200mg, administered after usual dose of Prednisolone or Beclomethasone.	[23,25,45]
Bactrim (co-trimoxazole)	Tablet	960 mg twice daily for 7 days	[23,25]
Amoxicillin	Tablet	500 mg 3 times a day for 7 days.	[23,25]

Table 4-10: Assumptions used to calculate the unit cost for asthma and COPD in Malawi

Assumptions	Value	Source
Exchange rate (MWK to US$, 2020)	749.527	[42]
GDP deflator (2020)	125.552	[41]
Discount rate	3%	
Useful life of capital costs (in years)		
Consumables (stationery etc)	3	
Medical consumables (syringe, reagents etc)	3	
Medical devices (Electronic sphygmomanometer)	3	
Laboratory equipment	10	
Vehicles	10	
Buildings	30	
Furniture	5	

4.6.5 Health cost per patient by disease

Table 4-11 and Table 4-12 provide the annual costs for participants with asthma or COPD at QECH. The annual cost for a participant with asthma is 81,140 MWK (bootstrap 95% CI: 64970–98749) (US$ 108; bootstrap 95% CI: 87–132). Annual per participant with mild asthma cost is 41,423 MWK (bootstrap 95% CI: 31963–60233) (US$ 55; bootstrap 95% CI: 43–80.) while those with moderate/severe asthma is 101030 MWK (bootstrap 95% CI: 86868–119850) (US$ 135; bootstrap 95% CI: 116–160). In those participants with spirometry consistent with COPD, the annual cost of a participant with COPD 107477 MWK (bootstrap 95% CI: 92648–123753) (US$ 143; bootstrap 95% CI: 124–165). For those with mild COPD the annual per participant cost is 72518 MWK (bootstrap 95% CI: 60402–96749) (US$ 97; bootstrap 95% CI: 81–129) while those with moderate/severe COPD is 123771 MWK (bootstrap 95% CI: 112453–140723) (US$ 165; bootstrap 95% CI: 150– 188). Excluding admission costs, unit annual per participant cost for those with mild asthma is 31,9623 MWK (US$ 43) while those with moderate/severe asthma is 77,445 MWK (US$ 103), and those with mild COPD is 60,402MWK (US$ 81) and for moderate/severe COPD is 112,453 MWK (US$ 150). The difference in costs of those with mild asthma compared to those with mild COPD is primarily a consequence of using spirometry to diagnose COPD. The COPD diagnostic unit per participant total cost that we estimated from our study data were 35,572 MWK (US$ 47), 96% (US$ 45) of which is attributable to the annualised cost of purchasing the portable spirometer for our study. Medication costs were almost six times greater in the moderate/severe cases compared to the mild cases in both those with the asthma or COPD. In those with mild asthma, medication costs accounted for 10.4% and outpatient visits accounted for 43.6% of the total cost, whilst for those with moderate/severe asthma, medication costs

accounted for 24.7% with outpatient visits accounting for 35.7% of the total costs. For those with COPD, medication costs accounted for 5.6%, our estimated diagnosis accounted for 49.1% and outpatient visits accounted for 24.9% of the total costs, whilst for those with moderate/severe COPD, medication cost accounted for 20.4%, diagnosis accounted for 28.7% and outpatient visits accounted for 29.1% of the total cost.

Table 4-11: Annual health service per participant cost of asthma in Malawi.

Health service used and cost	**Mild asthma**		**Total costs as a % of bootstrap mean cost**	**Moderate/Severe asthma**		**Total costs as a % of bootstrap mean cost**
Household (Patient costs)	MWK	US$		MWK	US$	
Drug costs						
Salbutamol	2,511.01	3.35		5,022.01	6.70	
Aminophylline				2,922.59	3.90	
Beclomethasone				9,697.68	12.94	
Prednisolone				1,813.33	2.42	
Hydrocortisone				1,233.56	1.65	
Bactrim (co-trimoxazole)	372.44	0.50		521.42	0.70	
Amoxicillin	677.87	0.90		949.01	1.27	
Out-of-pocket drug cost	750.00	1.00		2,800.00	3.74	
Total drug costs – Household costs	**4,311.31**	**5.75**	**10.4%**	**24,959.60**	**33.30**	**24.7%**
Outpatient costs						
Transport	300.00	0.40		1,650.00	2.20	
Food	122.22	0.16		550.00	0.73	
Test, consultation, administrative & other costs	527.78	0.70		1,305.56	1.74	
Total out-of-pocket outpatient costs	**950.00**	**1.27**	**2.3%**	**3,505.56**	**4.68**	**3.5%**
Productivity losses						

Time loss due to illness costs	8,653.85	11.55		12,884.62	17.19	
Total household perspective costs (patient costs)	**13,915.16**	**18.57**	**33.1%**	**41,349.78**	**55.17**	**40.9%**
Health system costs						
Outpatients visit costs[&]						
Medical equipment	440.11	0.59		880.22	1.18	
Furnishing	956.93	1.28		956.93	1.28	
Building and maintenance	1291.55	1.72		1291.55	1.72	
Staff costs	15358.98	20.49		32967.45	43.98	
Diagnosis costs	–	–				
Total health system perspective outpatient cost	**18,047.58**	**24.08**	**43.6%**	**36,096.15**	**48.16**	**35.7%**
Total costs without admission costs	**31,962.73**	**42.64**	**77.1%**	**77,444.93**	**103.33**	**76.7%**
Hospital Admission costs	84,810.69	113.15		84,810.69	113.15	
Total costs including admission costs	**116,773.43**	**115.80**		**162,255.62**	**216.48**	
Mean cost from the bootstrap resamples total cost (SD)[Ø]	**41,423.18 (8,922.45)**	**55.27 (11.90)**		**101,010.70 (8945.89)**	**134.77 (11.94)**	

[Ø] Cost obtained from the 100,000 bootstrap resamples. Provides a more precise cost estimate.

[&] Outpatient visit is the unscheduled emergency care received by the patients with acute/sub-acute exacerbation of respiratory symptoms at health facilities

Table 4-12: Annual health service per participant cost of chronic obstructive pulmonary disease (COPD) in Malawi.

Health service used and cost	**Mild COPD**		**Total costs as a % of bootstrap mean cost**	**Moderate/Severe COPD**		**Total costs as a % of bootstrap mean cost**
Patient costs	MWK	US$		MWK	US$	
Drug costs						
Salbutamol	2,511.01	3.35		5,022.01	6.70	
Aminophylline				2,922.59	3.90	
Beclomethasone				9,697.68	12.94	
Prednisolone				1,813.33	2.42	
Hydrocortisone				1,233.56	1.65	
Bactrim (co-trimoxazole)	372.44	0.50		521.42	0.70	
Amoxicillin	677.87	0.90		949.01	1.27	
Out-of-pocket drug cost	500.00	0.67		3,050.00	4.07	
Total drug costs– Household costs	**4,061.31**	**5.42**	**5.6%**	**25,209.60**	**33.63**	**20.4%**
Outpatient costs						
Transport	550.00	0.73		1,226.66	1.64	
Food	135.71	0.18		193.34	0.26	
Test, consultation, administrative & other costs	420.00	0.56		1,272.06	1.70	
Total out-of-pocket outpatient costs	**1,105.71**	**1.48**	**1.5%**	**2,692.06**	**3.59**	**2.2%**
Productivity losses						
Time loss due to illness costs	2,115.38	2.82		12,884.62	17.19	
Total household perspective costs (patient costs)	**7,282.41**	**9.72**	**10.0%**	**40,786.28**	**54.42**	**33.0%**

Health system costs						
Outpatients visit costs[&]						
Medical equipment	440.11	0.59		880.22	1.18	
Furnishing	956.93	1.28		956.93	1.28	
Building and maintenance	1291.55	1.72		1291.55	1.72	
Staff costs	15358.98	20.49		32967.45	43.98	
Total health system perspective outpatient cost	**18,047.58**	**24.08**	**24.9%**	**36,095.15**	**48.16**	**29.1%**
Diagnosis costs[#]	35,571.60	47.46	49.1%	35,571.60	47.46	28.7%
Total costs without admission costs	**60,401.58**	**80.59**	**83.3%**	**112,453.03**	**150.03**	**90.9%**
Admission costs	84,810.69	84,810.69		84,810.69	113.15	
Total costs including admission costs	**145,212.27**	**193.74**		**197,263.72**	**263.18**	
Mean cost from the bootstrap resamples total cost(SD)[Ø]	**72,517.51 (11,196.34)**	**96.75 (14.94)**		**123,770.50 (7,410.74)**	**165.13 (9.89)**	

[Ø] Cost obtained from the 100,000 bootstrap resamples. Provides a more precise cost estimate.

[&] Outpatient visit is the unscheduled emergency care received by the patients with acute/sub-acute exacerbation of respiratory symptoms at health facilities.

[#] Estimated from Chikwawa lung health cohort study[6] data. Service not widely provided.

4.6.6 Unmet need and cost of service provision in the cohort

Unmet need for healthcare was defined as the need for access to adequate healthcare by either; a) patients with untreated disease as those who did not access a health facility while having wheeze symptoms consistent with asthma or spirometry consistent with COPD or, b) patients with suboptimal access to asthma/COPD care as those who accessed a health facility but did not receive long term respiratory medication or healthcare. Using medication usage and reported doctor diagnosis of asthma and/or spirometric evidence of COPD (see Table 4-7 and Table 4-8) we estimated the prevalence of unmet need in the participants; a) who did not access a health facility (n=1267) while having wheeze symptoms consistent with asthma or spirometry consistent with COPD and b) accessed a health facility (n=226) but received suboptimal care by receiving no long-term respiratory medication. We used the estimated prevalence to estimate the accompanying total cost to address the asthma or COPD care in our cohort (n=1493). Of those that did not access a health facility, 5.7% (n=72) participants had symptoms consistent with asthma, whilst 19.5% (n=247) had spirometry consistent with COPD. Of those who accessed a health facility, 11.9% (n=27) participants had symptoms consistent with asthma, whilst 9.7% (n=22) had spirometry consistent with COPD. In the entire cohort, only 7 participants (7.1% of those with consistent wheeze symptoms) had an established doctor diagnosis of asthma while COPD had not been established by a doctor in any of the participants. In those who accessed a health facility with a wheeze symptom consistent with asthma, only 7 participants (25.9%) had used medication for their respiratory condition, whilst in those with spirometry consistent with COPD only 5 participants (22.7%) used medication for their respiratory condition. Most of the participants reported receiving no medication or health care. Of those that did not access a health facility, 95.8% of the participants with asthma had an unmet need with 97.2% of the participants with spirometry

consistent with COPD having an unmet need. Of those that accessed a health facility, 74.1% of the participants with asthma had an unmet need with 77.3% of the participants with spirometry consistent with COPD an unmet need. In our entire cohort, 89.9% of the participants with asthma had an unmet need with 95.5% of the participants with spirometry consistent with COPD an unmet need (see Table 4-13).

To illustrate the financial unmet needs of asthma and COPD the mean per patient cost of asthma and COPD were US$108 and US$143, however 73% of those with symptoms consistent with asthma and 92% of those with spirometry consistent with COPD have no health facility contact and incurred no costs.

Table 4-13: Prevalence of unmet need and budget cost required in out cohort of patients with asthma and COPD.

Characteristic	**Percentage with an unmet need[ø]**	**Total cost (95% CI), US$**
Participants with access to health facilities but getting suboptimal care.		
Asthma, n=27	74.1% (20/27)	2165 (1734 – 2635)
COPD, n=22	77.3% (17/22)	2438 (2101 – 2807)
Sum costs		4603 (3835 – 5442)
Participants who did not access a health facility		
Asthma, n= 72	95.8% (69/72)	7469 (5981 – 9091)
COPD, n=247	97.2% (240/247)	34414 (29666 – 39626)
Sum costs		41883 (35647 – 48717)

[ø] Defined as having a wheeze symptom consistent with asthma or spirometry consistent with COPD for which no medication received

4.7 Discussion

This study has estimated the annual cost of asthma and COPD case management and care at a hospital in Malawi with a mixed rural/urban catchment area, further insight was obtained by using a general population based respiratory survey from the hospital catchment area that included measurement of lung function using spirometry. Specifically, we present unit cost for the people with mild or moderate/severe asthma and mild or moderate/severe COPD. This detailed costing study shows that per capita asthma costs are US$108 per year while COPD costs are US$143 per year. Whilst these costs are comparable to other LMICs[25,48], they are significantly lower than the costs incurred in HIC settings[16]. Our findings show that the costs for asthma care are driven by hospital in- and out-patient episodes to treat acute/sub-acute exacerbations and that when compared with mild asthma, moderate/severe asthma is associated with an almost tripling of medication costs. For COPD care, costs are driven by diagnosis and in- and out-patient hospital episodes to treat acute/sub-acute exacerbations and when compared with mild COPD, moderate/severe COPD is associated with an almost quadrupling of medication costs. We found that transport and food cost are not major cost drivers for asthma or COPD with none of these input costs contributing more than 5% of the total costs. The general population cohort study shows that most of the people with wheeze symptomatic of asthma or with spirometry indicative of COPD using the healthcare system and incurring health related costs ($108 and $143) had not been formally diagnosed with asthma (74%) or COPD (100%). In addition, those with asthma or COPD and health facility contact are a minority: 73% of those with symptoms consistent with asthma and 92% of those with spirometry consistent with COPD have no health facility contact and incur no costs.

This study identified considerable unmet respiratory health need in the general population: 89.9% of those with symptoms consistent with asthma and 95.5% of those with spirometry

consistent with COPD had unmet respiratory health care needs through failure to attend health care facilities with exacerbations, lack of long-term medication and lack of long-term follow-up. Even those who attended health facilities for exacerbations had unmet healthcare needs (74.1% asthma, 77.3% COPD) because of a lack of long-term medication and follow-up. The financial consequences of universal health coverage by meeting the unmet need of those with asthma or COPD who do not currently engage with the health system and incur costs would be considerable because they greatly outnumber (2-3 fold for asthma, 11-12 fold for COPD) those who currently engage with the health system and incur costs. The per capita cost of universal coverage is likely to be less than the US$ 108 for asthma and US$ 143 for COPD reported here because they appear to have less severe disease (fewer symptoms, better lung function). Nevertheless the per capita cost of universal coverage for those with asthma or COPD who do not currently engage with the health system is likely to exceed the average per-capita health expenditure in Malawi of US$ 35 per year[49].

Malawi will need to mobilise resources to meet the cost of asthma and COPD care as our study found the lowest cost to be that of mild asthma of US$ 55 (bootstrap 95% CI: 43–80). Based on our findings, strategies to strengthen and expand access to diagnosis and medication for asthma and COPD[50] should be considered. If effectively implemented these will reduce per-capita diagnostic costs and the number of acute/sub-acute exacerbations needing hospital treatment that currently drive asthma/COPD costs. However, the Malawi per-capita health expenditure of US$35 only covers a year supply of the minimum recommended treatment of beclomethasone[36] that will reduce asthma exacerbations and their associated costs by 50%[51]. Further reductions in exacerbation frequency are achievable using combined Maintenance and Reliver Therapy (MART) as recommended by GINA[33,52], however treatment costs are higher and likely to exceed cost savings associated with reduced

exacerbations. For COPD, a management strategy shown to reduce the need for hospital-based treatment of COPD exacerbation by 50%, is the use of self-management plans that include anticipatory 'emergency packs' of antibiotics and corticosteroids at home[53]. This relatively cheap intervention (<US$5) is well within the per-capita health expenditure for Malawi and could be used to offset asthma care costs, however at present it is not implementable because very few of our general population survey with spirometric evidence of COPD and exacerbations had received a formal diagnosis of COPD. Use of combined inhaled therapies in LMIC settings to reduce COPD exacerbations[54,55] and their associated costs by 20-30% will need careful evaluation to ensure their greater costs are justified, superficially it would seem likely that these inhaled formulations are unviable in an LMIC setting unless supplied at a greatly reduced cost.

As expected, we found a higher prevalence of wheeze symptoms consistent with current asthma[34] and spirometry consistent with COPD than self-reports of diagnosis of asthma and COPD made by a healthcare provider. This was because we used an objective validated measure of ventilatory function[6,12] to identify those with COPD and the use of comprehensive reporting of respiratory symptoms by the participants to identify those with symptoms consistent with current asthma. The validity of the spirometry screening to diagnose COPD is observed in the comparable measures of spirometric values from the different patient cohorts from both rural and urban cohorts used in our study. While spirometry screening and diagnosis for COPD has been shown to be cost-effective compared to questionnaire screening in a previous study[56] and has been recommended by GOLD[31,32], spirometry services were not available at the tertiary facility in which this study was conducted. This study has reported the unit cost for spirometry diagnosis of US$ 47, a large proportion of which (96%) is attributable to the annualised cost of purchasing the portable spirometer device. This per capita cost could

be a hindrance to the increased adoption of spirometric diagnosis service but could be reduced by increased use (likely resulting in economies of scale) and centralisation of service. With this diagnostic limitation and limited pharmaceutical therapies[57] we have provided the costs for current asthma and COPD care that appears to be underdiagnosed and undertreated. It should be noted that in those only 7.1% of people with symptoms consistent with current asthma reported a diagnosis of asthma and in those who accessed a health facility 28% of people with moderate/severe asthma who had exacerbated in the previous year were on asthma medication, the 72% not on asthma medication, in addition to those who did not access a health facility will be at high risk of further exacerbations and will incur further costs. The use of a general population study of respiratory symptoms and lung function allowed us to identify the large proportion of symptomatic underdiagnosed and undertreated people with no contact with the healthcare services that would not have been identified by restricting the study to healthcare facilities or to those identified through diagnosis by a physician, alongside this we have provided the proportion of unmet need in both the asthmatic and COPD participants.

The Malawian Ministry of Health established the noncommunicable disease and injuries (NCDI) poverty commission in 2016[30] in order to address the NCDI crisis in the country. The estimated unit cost values of COPD and asthma case management reported in this study will be useful in deciding which cost-effective interventions could best be implemented within the Malawian health system and scaled up to address the burden of CRDs in Malawi and other countries with similar contexts. These estimates will also be useful for parameterising cost-effective and economic models for asthma and COPD interventions in LMICs.

4.7.1 Limitations

This study has several limitations. The sample size from which we estimated the patient perspective unit costs was relatively small. In those participants who accessed the health facility and incurred an out-of-pocket cost, we identified 49 (asthma, n=27; COPD, n=22) people who either had asthma or COPD using wheeze symptoms and spirometric measurement. Similarly, the number of patients diagnosed with asthma or COPD by a physician was small. This would likely result in an under representation of the general population distribution and may therefore limit the generalizability of our findings. We used a non-parametric bootstrap analysis so as to provide better estimates of the uncertainties resulting from the small sample and the skewness inherent in most cost data[39,58]. A costing study having a large randomly selected sample drawn from participants in Malawi should provide more accurate and precise cost estimates. In addition, the costs presented are from a public tertiary hospital, do not include children, and getting precise data on productivity losses, salbutamol and beclomethasone use was challenging leading to using conservative estimates thus the estimated total costs per patient reported are most likely an underestimate. We relied on self-reported symptoms, exacerbation and hospital use for the patient perspective. Although we tried to triangulate some of the asthmatic and COPD patients from the hospital while conducting the costing study at the chest clinic, recall bias is still a potential limitation. We also suspect that stigma associated with asthma and COPD resulted in underdiagnosis of these conditions, we noted that some participants with wheezing symptoms who reported no exacerbations in the previous year, reported in and out-patient episodes to treat ‘lung problems’.

4.8 Conclusions

In conclusion, this study has used a mixture of hospital and general population based studies to report current economic costs for asthma and COPD care in an LMIC setting (Malawi). The estimated costs are substantial ranging from one and half time to about five times the average total per-capita health expenditure in Malawi. The major contributors of costs are in and out-patient hospital episodes to treat acute/sub-acute exacerbations and for COPD diagnostic services. Medication costs contribute 5-10% of costs, however there was evidence of substantial undertreatment for asthma and COPD. These findings justify continued efforts to mobilise resources for under resourced health system and research into finding sustainable diagnosis and management strategies to reduce exacerbations of asthma and COPD in sub-Saharan Africa.

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5 Treatment intervention strategies for asthma and chronic obstructive pulmonary disease in Malawi – economic evaluation based on a five-year population cohort.

5.1 Overview

This chapter provides the estimates of the long-term costs and effects of possible interventions in Malawi. Using a Markov model, this chapter evaluated the use of anticipatory 'emergency packs' of antibiotics and corticosteroids at home for COPD and inhaled beclomethasone and salbutamol for asthma compared to usual care as observed in the Malawian situation. The findings from this chapter specifically address the third objectives of my thesis of estimating the cost-effectiveness of selected key interventions for adults with airflow obstruction in Malawi. The chapter is yet to be published.

5.2 Role of the candidate

I developed the first version of the Markov model, conducted all the data analysis in this chapter, wrote the first version of the manuscript as a thesis chapter and will be the first author and corresponding author of the resultant manuscript. Revisions to the chapter were made with feedback, input, and guidance from my supervisors Graham Devereux, Louis W. Niessen, Angela Obasi and Jamie Rylance.

5.3 Abstract

5.3.1 Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are the most common chronic respiratory diseases. 90% of the deaths from COPD are in populations living in low- and middle- income settings (LMICs). This study evaluates the long-term costs and effects of possible interventions in Malawi and usefulness in similar settings.

5.3.2 Methods

A six-stage Markov model having four mutually exclusive disease states for patients with asthma or COPD in addition to a death state, and a healthy state named general population was developed to conduct a cost-effectiveness analysis over a patient's lifetime. Patients entered the model at the age of 35 from the general population state. We evaluated the use of anticipatory 'emergency packs' of antibiotics and corticosteroids at home for COPD and inhaled beclomethasone and salbutamol for asthma. Estimation of stage-specific probabilities, utilities and costs was based on Malawian cohort studies and lifetables. A discount rate of 3% was applied to costs. Probabilistic sensitivity analysis was used to assess the robustness of the results.

5.3.3 Results

The COPD intervention dominated usual care in the people with mild COPD while the incremental cost effectiveness ratios (ICERs) were US$ 72, US$ 102, and US$ 242 in people with mild asthma, moderate/severe asthma, and moderate/severe COPD respectively. The asthma intervention resulted in a life-years gain of 1.62 years and 1.29 years in the patients with mild asthma and moderate/severe asthma respectively while the COPD intervention resulted in a life-years gain of 3.49 years and 3.90 years in patients with mild COPD and

moderate/severe COPD respectively. Sensitivity analysis showed that uncertainty primarily originated from data on treatment cost especially in people with moderate/severe COPD.

5.3.4 Conclusion

Using a Markov model, we estimated the long-term cost effectiveness of an emergency pack intervention for COPD and widespread administration of inhaled beclomethasone and salbutamol for asthma. The COPD intervention was dominant in people with mild COPD while the in the people with moderate/severe COPD and people with asthma the ICER ranged from US$ 72 to US$ 241. The COPD intervention resulted in larger life expectancy gains compared to the asthma intervention. In the univariate sensitivity analyses, the cost of managing moderate/severe COPD had the highest impact on the uncertainty in the model. This study describes the structure of an asthma and COPD dynamic prevalence model that accounts for disease natural occurrence and history until death with input parameters drawn cohort studies conducted in Malawi.

5.4 Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are the most common chronic respiratory diseases (CRDs)[1]. An estimated 358 million people are affected by asthma and 174 million people by COPD,[2,3] with COPD accounting for an estimated 6% of all deaths worldwide[2,4] of which 90% are in populations living in low- and middle- income settings(LMICs)[5]. In LMICs the prevalence of asthma and COPD are increasing, probably because of increasing urbanisation and life expectancy[6]. It is well recognised and advocated that incurable CRDs such as asthma and COPD, once diagnosed, need long term treatment and clinical follow-up[7,8]. In LMICs, where resources are especially scarce, knowledge on the medium and long-term benefits[9,10] and health costs of interventions support prioritisation and provision of effective interventions, the design of crucial CRD health services and budgeting for lung programmes. In these policy contexts, decision-analytic modelling provides an evidence-based framework to estimate the lifetime health effects and costs of appropriate interventions and supports rational decision-making[11].

Several important economic modelling studies have been conducted in lung health, mainly in high income countries (HICs), to estimate disease progression and cost-effectiveness of emerging treatments strategies or technologies for COPD[12,13] and asthma[14]. Most of these were Markov models[12–14]. However, these studies are not easily transferable to LMIC settings due to differences in healthcare systems, health budgets, population demographics and CRD risk factor exposure[3,15–17]. It is therefore essential that studies are conducted in LMIC settings that assess the economic impact of the natural history and increasing prevalence of COPD and asthma and the adoption of suitable interventions to enable better planning and resource allocation. Due to the long-term nature of treatment options for asthma and COPD resulting in uncertainty[11,18], estimating the costs, outcomes and cost-effectiveness of possible

intervention options will require the use of decision-analytic modelling to forecast their lifetime economic costs, health-related quality of life (HRQoL), efficacy and effectiveness outcomes.

We therefore set out to develop a Markov model for COPD and asthma using empirical cohort data from Malawi. Its aim is to evaluate the costs and effects of possible interventions in Malawi and usefulness in similar settings. To account for the natural history in the model, we included the effects of exacerbations driving health care costs through admissions, morbidity, and excess mortality; and provided for a probabilistic sensitivity analysis facilitating state-of-the-art techniques. The analyses focused on cost-effectiveness computations on the implementation of those interventions that are shown to reduce exacerbation rates in COPD: 1) anticipatory 'emergency packs' of antibiotics and corticosteroids at home[19]; and in asthma: 2) inhaled beclomethasone[20–22]. The analyses compared the impact of these interventions against usual care as observed in the Malawian situation, as control. The input data to parametrize the model were drawn from several cohort studies conducted in Malawi that quantified the prevalence of COPD or asthma, age-related changes over time, their associated HRQoL and their societal costs[16,23–25].

5.5 Methods

5.5.1 Model aims and description

The economic model was developed to provide healthcare policy makers in LMIC settings with a tool to generate evidence on the cost-effectiveness of treatment interventions and health packages for asthma and COPD whilst accounting for the natural disease history and population-level occurrence until death from lung disease. It therefore aims to describe the morbidity and mortality over patient lifetimes, including the disease severity, rates of asthma and COPD exacerbations as major drivers of healthcare expenditure, summarized by health-adjusted life expectancy and lifetime health costs by age.

We constructed the Markov model to have four mutually exclusive health states for patients with asthma or COPD, reflecting disease severity (see Figure 5-1) and adapted from previously published were Markov models[12–14] used HICs but parametrised with appropriate data from Malawi. The health states distinguished are mild asthma, moderate/severe asthma, mild COPD, moderate/severe COPD, and an absorbing state of death. The structure of the model was guided by research questions and informed by previous economic models used in the analysis of moderate to severe asthma and COPD[14] with asthma or COPD severity based on recommendations from the Global Initiative for Chronic Obstructive lung disease (GOLD)[9], the American Thoracic Society (ATS)/ European Respiratory Society(ERS)[26], and the Global initiative for asthma (GINA)[10]. Lung function parameters were compared with appropriate GLI 2012 predictive equations[27].

The empirical data in Malawi shows that most of the people with documented evidence of asthma/COPD, lack a clinical diagnosed COPD or asthma[16,17,23,28–30].Therefore, the following operational definitions were selected. We used the spirometric measures of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) to define COPD, with COPD being

defined as post-bronchodilator FEV_1/FVC<lower limit of normal (LLN)[26,31]. COPD severity was defined by FEV_1 with mild COPD being z-score ≥ -2 and moderate/severe COPD being z-score of <–2 irrespective of exacerbations leading to outpatient care or admission[26,31]. Z-scores were preferred to define COPD severity as they account for the age, sex and height related biases that arise from using only the GOLD criterion[9,31]. For asthma, current asthma comprised those who reported the pathognomonic symptom 'wheezing' over the last 12 months[10,32], with mild asthma being defined as those with asthma and no acute exacerbations in the previous year and moderate/severe asthma being defined as those with asthma and one or more acute exacerbation in the previous year leading to outpatient care or admission [10,32].

The baseline model scenario represents the major clinical characteristics and epidemiological occurrence in 2020 in the Malawian health system where lung disease is under-diagnosis, therefore, does not include the asthma COPD overlap syndrome (ACOS)[33] as well as the physiological evidence of COPD in people with asthma, for lack of age-specific data at the population level. Figure 5-1 represents the structure of the model. The cycle length of the model is one year, with the participants entering the model at the age of 35 years, aging in annual steps, until a maximum lifetime horizon is reached, with the lifetime age limit of 95 years.

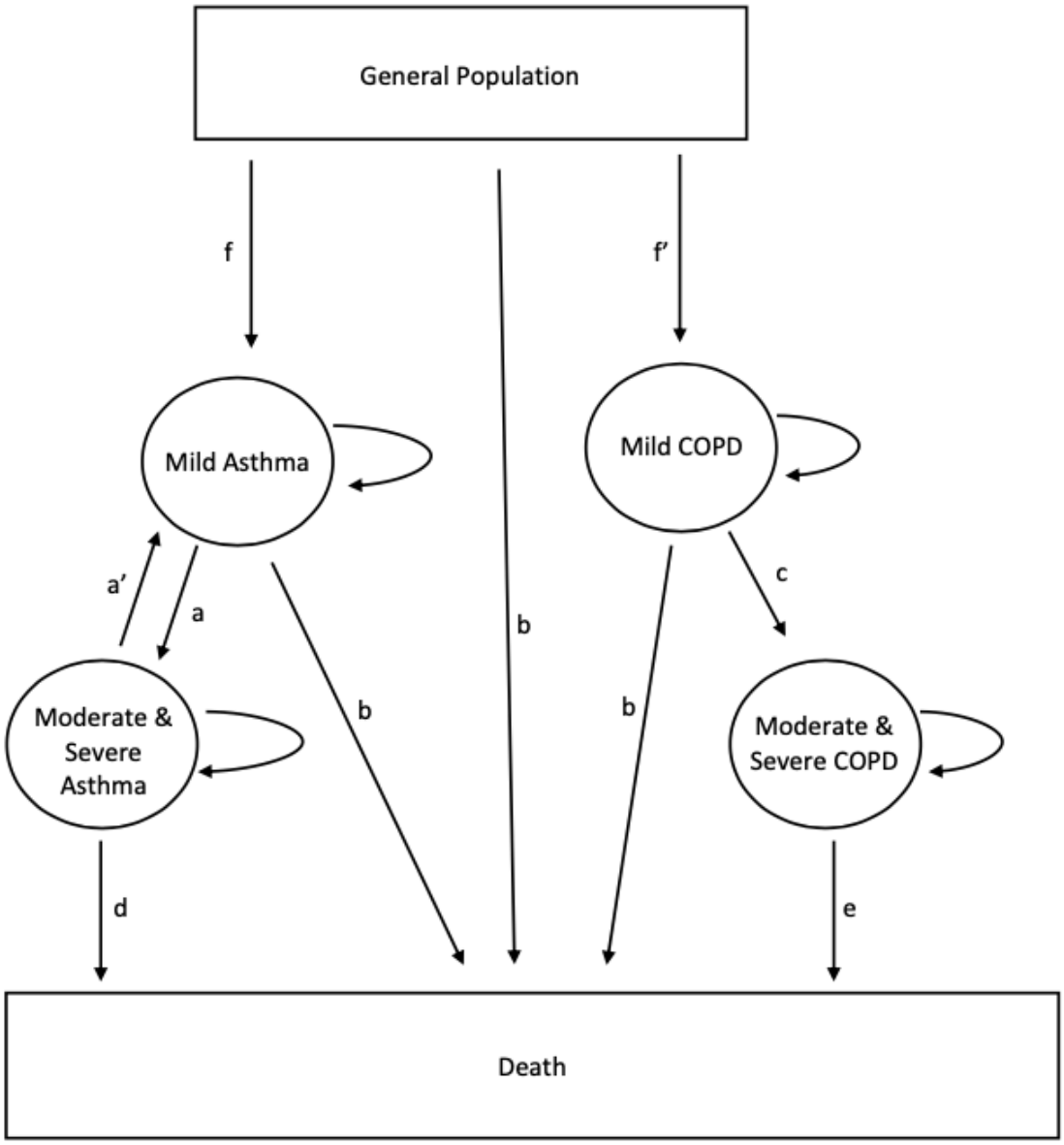

Figure 5-1: **Structure of the Markov model of asthma or COPD prevalence and progression in Malawi**. The arrows show the transition permitted from one health state to the next in each cycle. Death is an absorbing state. Asthma and COPD cases are drawn from the general population using their respective person-time incidence rates.

5.5.2 Definitions of transition probabilities

The transition probability estimates represented in the figure; a) probability of having an acute exacerbation in the year when in the mild asthma state, a') probability of not having an acute exacerbation in the year when in the moderate/severe asthma state, and, hence, an

absence of lung-specific mortality. Assumed to be approximately equal to a, b) age specific general mortality probability, c) a COPD transition probability based on the annual decline in lung function, d) age-specific excess mortality probability due to asthma, e) age-specific excess mortality probability due to COPD, f) asthma person-time incidence rate and f') COPD person-time incidence rate.

5.5.3 Estimation of the transition probabilities in the lung health model

5.5.3.1 Natural disease history – baseline

In order to use Malawi specific data on lung function decline, estimated lung function was calculated from data collected within the Chikwawa lung health cohort[23,28,29]. With 1232 participants followed over five years, we used linear mixed-effects models to estimate the decline of FEV_1 to be 53.4 ml/year equating to an FEV_1 z-score decline of 0.068 per year[16]. In the first year of simulation published cohort studies are used to estimate the prevalence for asthma (estimated prevalence: 3.7%) and COPD (prevalence estimate: 12.4%)[16,17,23,28–30] are used to distribute the cohort over the asthma or COPD health states. Subsequently, the severity stages of COPD were estimated from the expected annual decline in FEV_1 z-score and patient age whilst the severity stages of asthma were estimated from the number of exacerbations in a year and patient characteristics.

The model starts with patients receiving the usual care for diagnosed asthma or COPD in Malawi drawn from adults of 35 years at baseline from the general population. Table 5-1 reports the main input parameters for the baseline scenario.

The transitions from COPD disease stages in the model are assumed to be unidirectional where participants can only transition from mild to moderate/severe states[34–36]. For asthma disease stages, the transition from mild to moderate/severe states was bidirectional based

on occurrence of acute exacerbation[37]. Consequently, in sum, within the model, a net proportion of mild asthma patients will experience an acute exacerbation and move to moderate/severe asthma state, and these are matched by patients with moderate/severe asthma not experiencing an acute exacerbation in the year and thus moving to mild asthma health state.

Table 5-1: Main input parameters, values and source for the asthma or COPD disease natural disease history model for Malawi.

	Mild asthma	Moderate/severe Asthma	Mild COPD	Moderate/severe COPD	Source of the data
Prevalence as a percentage of general population at 35 years*.	1.48%	2.22%	3.95%	8.45%	16,17,23,28–30
Incidence rate in general population at 35 years&.	0.0023	0.0035	0.0149	0.0005	16,23,28,29
Annual transition probabilities					
Estimated transition probability from mild to moderate/severe COPD calculated from annual decline in FEV_1 z-score (at 35 years)	–	–	0.0657		23,28,29
Incidence of exacerbation as a percentage of general population at 35 years*: informs the transition probability from mild to moderate/severe asthma	3.98 per 100 person-years		–	–	16,23,28,29
Age specific death probability of death at 35 years#	0.0009	0.0014	0.0009	0.0014	38–41
Asthma or COPD related healthcare costs (US$ 2020)	55 (43 – 80)	135 (116 – 160)	97 (81 – 129)	165 (150 – 188)	Chapter 5
Average annual exacerbation rate	0	1.72 (1.37 – 2.07)	0.86 (0.19 – 1.53)	1.60(1.10 – 2.10)	17,23,25
SF-6D Utilities[16].	0.754(0.678 – 0.830)	0.676(0.606 – 0.747)	0.727(0.634 – 0.820)	0.669(0.609 – 0.729)	16

* Data from the year 2020, the first year of the simulation.

&The incidence has been estimated from the number of people who developed asthma or COPD between 2014 (when the baseline data was collected) and 2019/20 (when follow-up data was collected).

The age at entry into the model is 35 years. The age-specific death rates from mild asthma and COPD have been obtained Malawian standard life tables[40].

5.5.4 Baseline exacerbations

The baseline rate of exacerbation was calculated from the three lung health cohort studies that have been conducted in Malawi[17,23,25]. For mild asthma as defined earlier, mild asthma was assumed to be controlled with no exacerbations per year whilst moderate/severe asthma was calculated to have an exacerbation rate of 1.72 (95% CI: 1.37 – 2.07) per year, whilst for COPD, the rate of exacerbation per year of mild COPD was estimated to be 0.86 (95% CI: 0.19 – 1.53)and 1.60(95% CI: 1.10 – 2.10)) for moderate/severe COPD.

5.5.5 Mortality

Using published Malawian general population data and lifetables[38–40], we estimated the general population rate of death stratified by age. These baseline rates were adjusted to account for an increased risk of death attributable to being in the moderate/severe asthma or COPD health states using published mortality risks for asthma and COPD[41] and validated with verbal autopsy data we collected in our lung health cohort study conducted in Malawi[16,23]. The rates were used to estimate the annual transition probabilities to the death state used in the model using the following equation[42–44]:

$$p = 1 - e^{-rt}$$

where:

$$p\ is\ the\ probability\ estimate.$$

$$e^{-rt}\ is\ the\ exponential\ function\ of\ the\ rate\ (r)\ and\ time(t).$$

$$The\ unit\ of\ time\ used\ for\ r\ and\ t\ in\ this\ model\ is\ 1\ year.$$

5.5.6 Health outcomes and costs

5.5.6.1 Health-related quality-of-life by disease state

We used data from a cohort study conducted in Malawi[16,23] and applied the validated Brazier SF–6D algorithm to obtain a summary preference-based health utility measure (HRQoL utility

score) that ranged from 0 (for death) to 1 (full health)[45]. The HRQoL score was in turn used in the calculation of quality-adjusted life year (QALYs) and cost per QALY ratios[11]. Each disease state had a baseline estimated health utility measure for stable disease and an estimated health utility measure due to the mean number of exacerbations per year.

5.5.6.2 Data on resource use and costs

Each disease state had two cost components: maintenance cost for stable disease per 1-year cycle and additional costs due to exacerbation. We estimated the cost from a societal perspective by summing the direct and indirect household and health perspective cost of each disease state and followed consolidated health economic evaluation reporting standards (CHEERS) guidelines[46]. Patient health resource use and costs were obtained from three cohort studies in southern Malawi[17,23,25]. Health provider resource use and costs were obtained in one of these studies[25], and a bespoke costing study at a chest clinic[23]. All cost were adjusted to 2020 values. Details on the cost estimation are provided in the preceding chapter and the annualized estimated are listed in the input Table 5-1, above.

5.5.7 Baseline scenarios and outcomes

The estimated cost for the baseline scenario was based on the cost of receiving the usual care of outpatient visits and inpatient admissions for acute exacerbations of asthma or COPD. The base case health effects and outcomes were summarized from estimated mean values over one years from published cost and effects data from lung health cohorts in Malawi[17,23,25], a costing study done in the previous chapter, while the HRQOL outcomes were estimated from a population cohort study[16]. The effects and costs were evaluated over a lifetime horizon. There wasn't a half-cycle correction[47] as a lifetime horizon was used. Discount rate was 3% for the health costs.

5.5.8 Intervention scenarios

For COPD, as an exemplar intervention, because of the expected primacy of exacerbations in driving healthcare costs we evaluated the cost-effectiveness of widespread use of a self-management plan that includes the keeping of anticipatory 'emergency packs' of antibiotics and corticosteroids at home that are self-administered in the early stages of exacerbation[19] compared with usual care for the different disease states. This intervention comprises of 15-30 minutes education (one off at the health centre) followed by 1–2 emergency packs a year each comprising prednisolone 30mg once a day for 7 days and an antibiotic, cotrimoxazole 960mg twice a day 7 days or amoxicillin 500mg three times a day for 7 days. The intervention was assumed to influence the outcomes for COPD by reducing the need for in/out-patient treatment of acute exacerbations by 43% based on systematic reviews of the impact of this intervention on acute exacerbations[19,48,49].

For asthma we evaluated the cost-effectiveness of widespread administration of inhaled beclomethasone (100µg/puff) and salbutamol (100µg/puff)[22,50] . For both beclomethasone and salbutamol, we assumed an average dose of 3 puffs a day to achieve control. The intervention was assumed to reduce the rate of experiencing an acute exacerbation needing an in/out-patient care by 51% based on systematic reviews of the impact of this intervention on acute exacerbations[22,50]. Table 5-2 provides a summary of the input data for the intervention scenarios modelled in this evaluation.

The asthma intervention was assumed to have a continuous effect on the HRQoL, and exacerbation reduced while the COPD was assumed to have a continuous effect on the exacerbation reduced.

Table 5-2: Input data for intervention scenarios (95% confidence intervals).

	Self-administered emergency packs	**Inhaled beclomethasone & salbutamol**	**Self-administered emergency packs + Inhaled beclomethasone & salbutamol**
Target population	Moderate or severe COPD.	Moderate or severe asthma	Moderate/ severe COPD or asthma
Total exacerbation leading to hospitalisation reduction	OR: 0.57 (0.43 – 0.75)	RR: 0.49 (0.38 – 0.63)	COPD: OR: 0.57 (0.43 – 0.75) Asthma: RR: 0.49 (0.38 – 0.63)
Annual intervention cost (2020 US$)#	104 (7 – 165)	80 (30 – 132)	

The lower limit in the annual expected cost of medication for stable condition. The upper limit is the expected cost of uncontrolled condition. The scenarios were evaluated in the sensitivity analysis to see how cost of interventions impacts the results.

5.5.9 Intervention exacerbations

Patients with asthma will have a reduced rate of exacerbations 51% in after proposed inhaled beclomethasone intervention compared to usual care were obtained from published systematic reviews[22,50] and reports from Global initiative for asthma (GINA) [10,20]. While for COPD, a 43% reduction of exacerbations after proposed emergency pack in were obtained from published systematic reviews[19,48,49] (see Table 5-2 above).

5.5.10 Probabilistic sensitivity analysis.

We assessed the uncertainty associated with model by conducting a probabilistic sensitivity analysis on the parameters for: prevalence for asthma and COPD, probabilities of disease natural history and exacerbation, HRQoL utility score for disease states and exacerbation, costs for disease states and exacerbation, and effectiveness of the interventions compared to usual care. We presented the variables with highest impact on the model uncertainty on a tornado graph. We used beta distribution for probabilities and HRQoL utility scores and gamma distribution for costs[11] as informed by our prior study data[16,17,23,25] to draw random values for parameters in our second order Monte Carlo simulation[11]. We ran 10,000

simulations to estimate the 95% uncertainty intervals around the effects and costs. The results were presented as points on the cost-effectiveness plane and in a cost-effectiveness acceptability curve using the net benefit approach[11]. All analysis was conducted using R v3·6·0 and MS Excel.

5.6 Results

5.6.1 Lifetime estimates of baseline usual care and intervention scenarios

In this analysis, the asthma and COPD simulated in the starting year of the model consisted of 10,000 participants drawn from a general Malawian population at 35 years at baseline. Table 5-3 reports the results from the usual care and intervention models. The average incremental cost per QALY gained for the people with mild asthma was US$ 71.77 and moderate/severe asthma was US$ 102.00. On the other hand, the COPD intervention was dominant (it cost less and had better effect outcomes) in people with mild COPD and US$ 241.46 for moderate/severe COPD. In the usual care cohort, resulted in 27.76 QALYS for mild asthma, 27.75 QALYS for moderate/severe asthma, 27.45 QALYS for mild COPD and 22.57 QALYS for moderate/severe COPD compared to the intervention cohort, where we estimated 31.93 QALYS for mild asthma, 31.49 QALYS for moderate/severe asthma, 31.83 QALYS for mild COPD and 25.56 QALYS for moderate/severe COPD. In all scenarios management of severe COPD was the costliest accounting for 73% of the total cost in the usual care cohort and 74% of the total cost in the intervention cohort.

Table 5-3: Average per patient lifetime costs, effects and cost effectiveness for the usual care compared to the asthma and COPD interventions.

Disease state	**Value**	**Costs (US$)**			**Effects(QALYS)**			**ICER (US$/QALY)**
		Usual care	Intervention	Difference	Usual care	Intervention	Difference	
Asthma								
Mild asthma	Mean value	92.59	391.89	299.30	27.76	31.93	4.17	71.77
Moderate/Severe asthma	Mean value	258.39	639.87	381.48	27.75	31.49	3.74	102.00
COPD								
Mild COPD	Mean value	681.20	593.76	-87.44	27.45	31.83	4.38	Dominant intervention
Moderate/Severe COPD	Mean value	1050.30	2013.74	963.44	22.57	25.56	3.99	241.46

Figure 5-2 shows the results of the univariate sensitivity analysis in the form of a tornado diagram displaying the effects of the uncertainty associated with individual parameter values on the net benefit of the intervention for a willingness to pay (WTP) of US$ 500. The cost of the disease specifically the cost of managing moderate/severe COPD is associated with the highest impact on the uncertainty in the model.

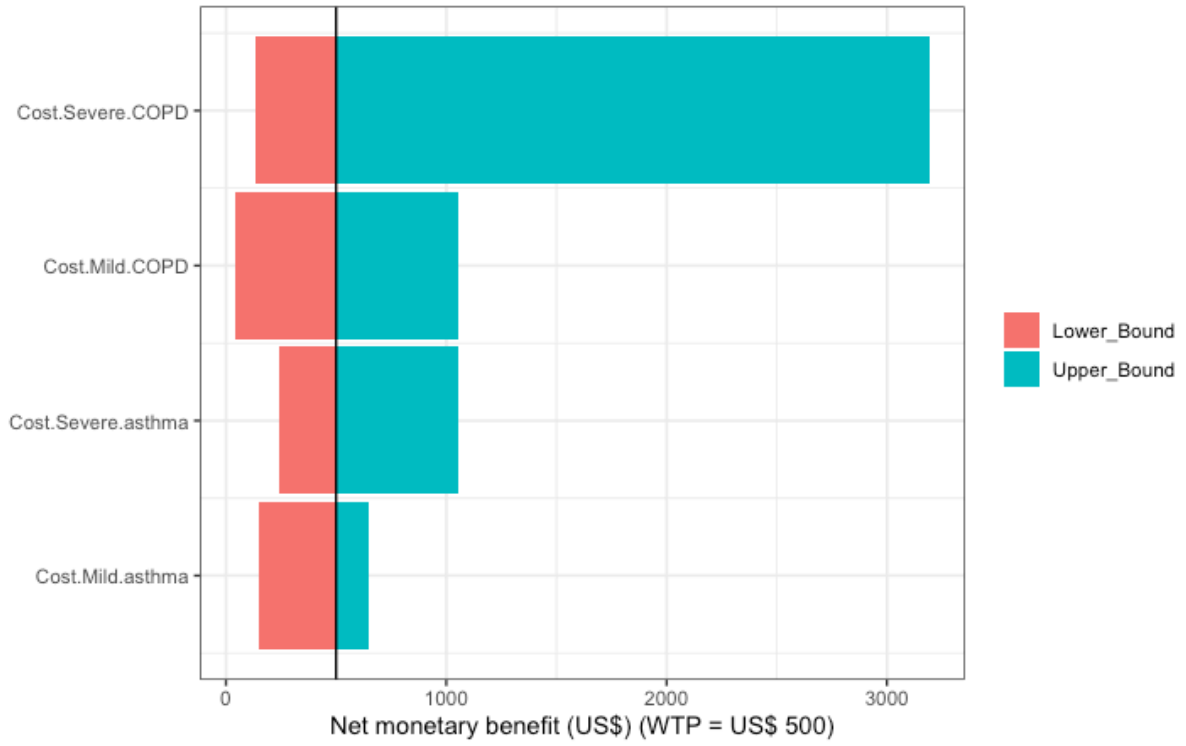

Figure 5-2: Tornado diagram for *the* univariate sensitivity analyses. The willingness to pay threshold is arbitrary but informed by the estimated GDP per capita value for Malawi in 2020.

5.6.2 Probabilistic sensitivity analysis.

The results from the probabilistic sensitivity analysis are shown in Figure 5-3 and Figure 5-4 on the cost-effectiveness plane and the cost effectiveness acceptability curve. These graphs which show the results of 10,000 simulations where we evaluated the cost-effectiveness of implementing the intervention on all patients with asthma and COPD independently compared to usual care. In almost all simulations, increased intervention costs are associated with increased number of exacerbations avoided and increased number of QALYs gained thus most of the simulations plotted are in the north-east quadrant. The ICER per QALY gained for COPD was US$ 69 while for the asthma intervention the mean ICER per QALY gained was US$ 246. We plotted a cost effectiveness acceptability curve (CEAC) to summarise the impact of uncertainty on the result of the asthma and COPD ICERs in relation to possible values of the cost-effectiveness thresholds. From the CEACs presented in Figure 5-4, compared to usual care the COPD intervention of emergency packs had an 80% probability of being cost-effective at a willingness-to-pay threshold of about US$ 110 per QALY while the asthma intervention of use of inhalers had an 80% probability of being cost-effective at a willingness-to-pay threshold of about US$ 400 per QALY for patients with asthma or COPD in the Malawian health system.

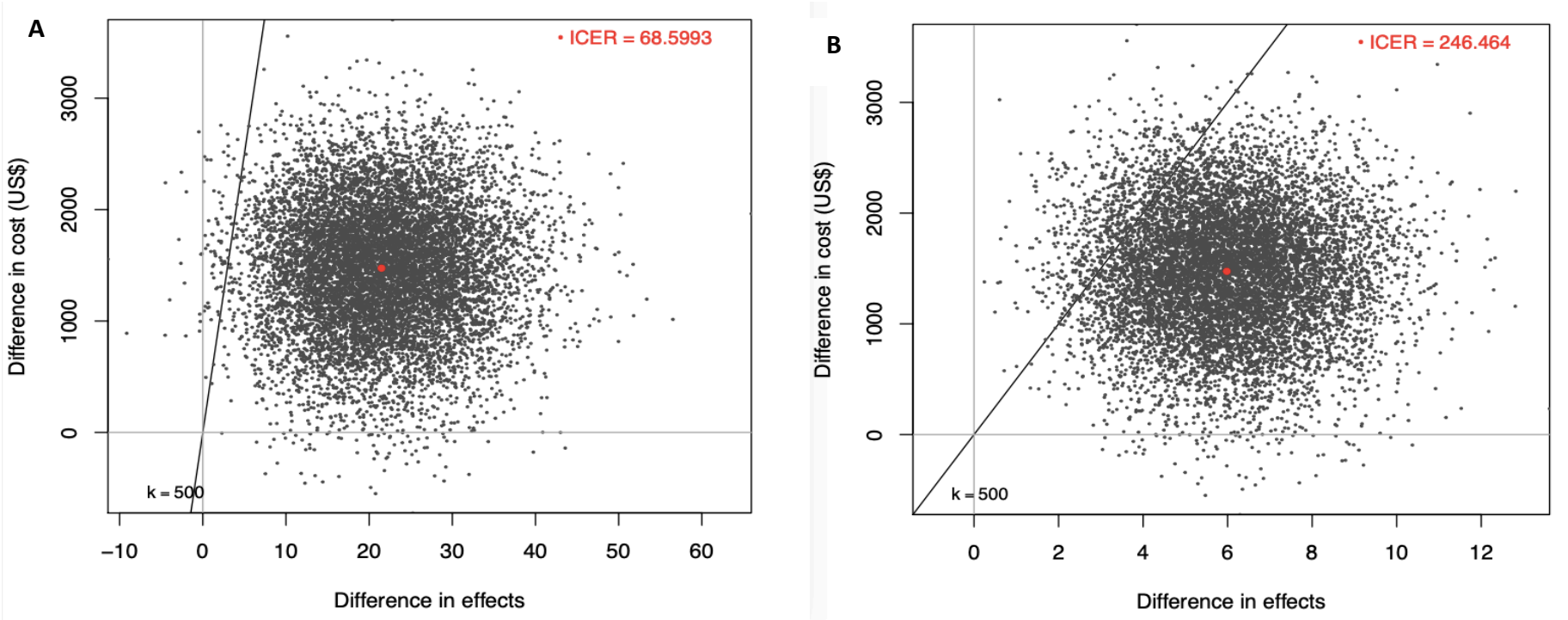

Figure 5-3: Cost effectiveness planes for implementation of the asthma and COPD interventions independently compared to usual care, lifetime time horizon. Values plotted are 10,000 second-order Monte Carlo simulations. A) Graph of QALYs gained with the COPD intervention. k shows an arbitrary selected threshold of US$500. B) Graph of number of QALYS gained with the asthma intervention. k shows the threshold of US$ 500, an arbitrary threshold informed by Malawi's GDP per capita.

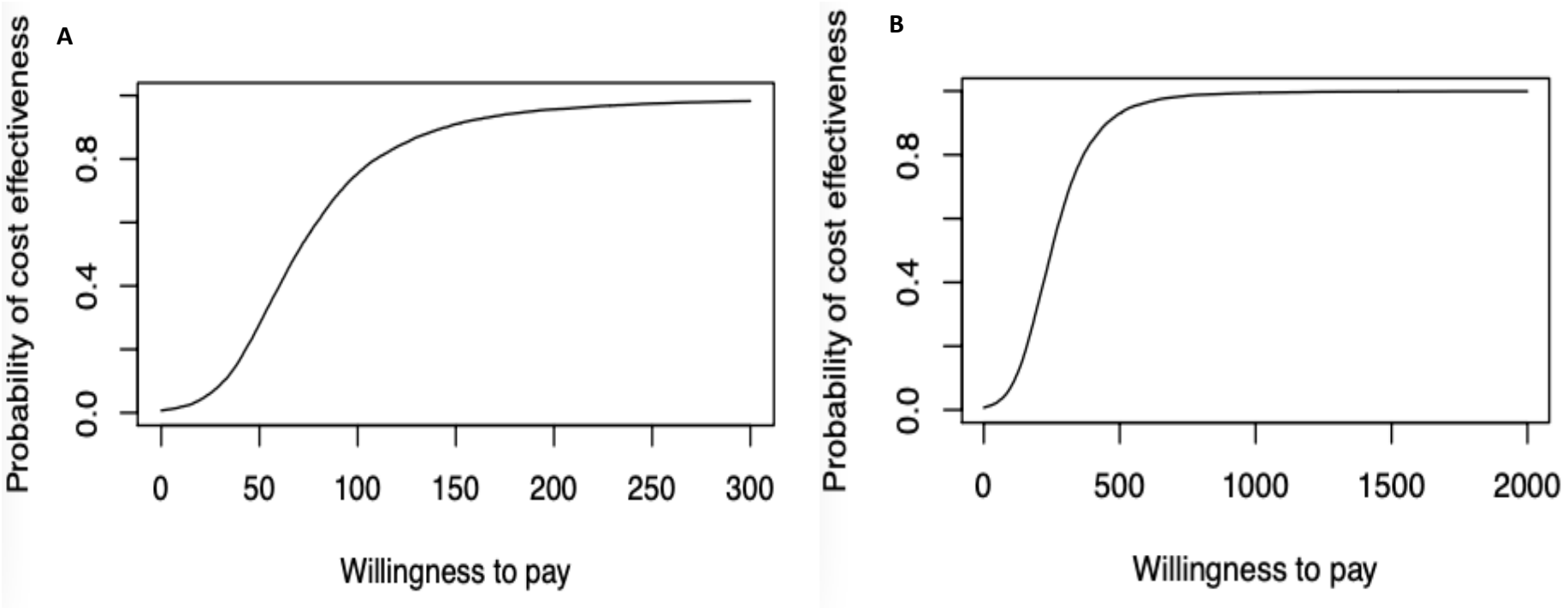

Figure 5-4: Cost-effectiveness acceptability curves for QALY gained for emergency packs for patients with COPD and use of inhalers in patients with asthma compared to usual care. A) COPD intervention CEAC B) Asthma intervention CEAC.

5.7 Discussion

In this chapter, a Markov model for asthma and COPD was developed and used to evaluate the long-term cost-effectiveness of an emergency pack intervention for COPD and wide-spread use of inhalers for asthma. In the base analysis, the COPD intervention dominated usual care in the people with mild COPD while the ICERs were US$ 72, US$ 102, and US$ 242 in people with mild asthma, moderate/severe asthma, and moderate/severe COPD respectively. The asthma intervention resulted in a life-years gain of 1.62 years and 1.29 years in the patients with mild asthma and moderate/severe asthma respectively while the COPD intervention resulted in a life-years gain of 3.49 years and 3.90 years in patients with mild COPD and moderate/severe COPD respectively. Secondly, the univariate sensitivity analysis found that the cost of managing moderate/severe COPD is associated with the highest impact on the uncertainty in the model.

This chapter describes a probabilistic dynamic prevalence-based cost-effectiveness model for asthma and COPD management in the Malawian health situation. A standout strength of the model is that the lung function and disease severity transition probabilities and outcome estimates have been derived from empirical data collected from cohort studies in Malawi[16,17,23,25] with demographic and mortality estimates estimated from published data by the Malawian government[38–40] thus strengthening the validity and credibility of the model for evidence use by healthcare policy makers in Malawi and similar settings.

We evaluated cost-effectiveness of the anticipatory 'emergency packs' of antibiotics and corticosteroids at home administered in the early stages of exacerbation[19] and widespread administration of inhaled beclomethasone (100µg/puff) and salbutamol (100µg/puff)[22,50] against usual care for COPD and asthma management respectively through both a deterministic and probabilistic analysis as an exemplar of our model. In our analyses,

increased cost resulted in an increase in the number of exacerbations averted, increased life expectancy and QALYs gained. While the gains for the intervention on life expectancy and QALYS were modest, the benefits were much more on the lifetime exacerbations averted. In the previous chapter we found that exacerbations are the main cost drivers for outpatient and inpatient care for asthma and COPD patients in Malawi. We found an 80% probability of being cost-effective at a willingness-to-pay threshold of about US$ 110 per QALY for the COPD intervention and US$ 400 per QALY for the asthma intervention. While both interventions are lower than the US$ 500 than we found best reflected the GDP per capita of Malawi[51], both interventions resulted in ICERs that would be out of reach for the Malawian health system as presently the average per-capita health expenditure in Malawi of US$ 35 per year[52]. However, given the limited budgets that constrain the Malawian health system, we would recommend that the COPD be implemented as it results in cost-savings in the long term and for mild COPD dominates usual care. We would also recommend that a budget impact analysis to be done to find ways to implement the asthma intervention while improving the quality of care in the Malawian health system.

There are several limitations of the cost-effectiveness modelling that we report here. The intervention effectiveness and mortality data were estimated from published systematic reviews[19,22] and government data[38–40]. To get better and more accurate data on the effectiveness of asthma and COPD interventions, lung health randomised control trials including health economic outcomes will need to be conducted in LMICs settings. In addition, to get better estimates for the mortality transition probabilities and health states, data from national registries will be vital. Although we validated our mortality transition probabilities with published studies, our study estimated probability estimate is likely to have different outcomes and an overestimate due to participant selection and participation.

The cohort studies that provided the cost estimates[17,23,25] had limited health use and cost data at the health facility due to underdiagnosis of asthma and COPD within the Malawian health system. Limited health facility use coupled with lack medication such as inhaled corticosteroids (ICS) and long-acting bronchodilators (LABA)[53,54] meant that we were unable to use the usual methods recommended by GINA[20,55] to grade asthma severity based on medication use. We used a non-parametric bootstrap analysis to provide better estimates of the uncertainties resulting from the small sample and the skewness inherent in most cost data[56,57] details of which are provided in the previous costing chapter. Alongside this, due to the limited data from health facilities on patients with an asthma or COPD diagnosis, the proportion of the patients in the various asthma or COPD severity states could not be estimated accurately. We therefore had two severity states per disease so that we could get useful estimates on disease severity from our available data. The use of disease natural history and prevalence of COPD and asthma in Malawi coupled with the thorough PSA component are evident strengths of this study.

5.8 Conclusions

In conclusion, using a Markov model we estimated the long-term cost effectiveness of an emergency pack intervention for COPD and widespread administration of inhaled beclomethasone and salbutamol for asthma. The COPD intervention was dominant in people with mild COPD while the in people with moderate/severe COPD and people with asthma the ICER ranged from US$ 72 to US$ 241 in the deterministic analysis. The COPD intervention resulted in larger life expectancy gains compared to the asthma intervention. In the univariate sensitivity analyses, cost of managing moderate/severe COPD had the highest impact on the uncertainty in the model.

This study describes the structure of an asthma and COPD dynamic prevalence model that accounts for disease natural occurrence and history until death with input parameters drawn cohort studies conducted in Malawi.

This model recommends that the COPD be implemented as it results in cost-savings in the long term, dominates usual care for patients with mild COPD and in the probabilistic analysis results in lower ICER outcomes for all patients with COPD. We would also recommend that a budget impact analysis to be done to find ways to implement the asthma intervention. The model can be used to provide healthcare policy makers with information about long-term costs and effects of interventions for asthma and/or COPD while accounting for uncertainty around the incremental costs and effectiveness by conducting probabilistic sensitivity analysis.

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6 Summary and future developments

Low- and middle- income countries (LMICs) have a sizable burden of the mortality and morbidity of chronic respiratory diseases (CRDs) (LMICs)[1–4], and a paucity of studies reporting and describing the health and economic burden of CRDs[5]. In these resource constrained settings, there is a pressing need to accurately estimate the CRD burden and provide evidence for cost-effective interventions so as to provide policymakers with evidence for planning and budgeting of selective interventions and mobilization of resources for scale-up of these interventions.

This PhD project was designed to estimate the health burden and economic cost of airflow obstruction from a societal perspective in a LMIC country setting. This research project was conducted specifically in Malawi since several community-based studies have documented a high prevalence of abnormal lung function, both obstructive and restrictive (low lung volumes)[6–10] but, hardly any studies have reported and described the health and economic burden of CRDs in this population[11]. The research questions that I aimed to answer in this PhD were: 1) What is the estimated health burden of airflow obstruction in Malawi? 2) What is the estimated current and future economic burden from a societal perspective, including households, of airflow obstruction in Malawi? and, 3) What is the estimated cost-effectiveness of selected key interventions for adults with airflow obstruction in Malawi? Using epidemiological and economic modelling approaches, I set about to address the research questions in this thesis. First, a cohort study was conducted in Chikwawa, southern Malawi, with the aim of estimating the health burden of obstruction in Malawi. The methods used and results from this cohort study are detailed in chapters two and three of this thesis. Following on, I conducted a health facility costing study embedded within cohort studies to estimate the current and future economic burden of the most prevalent obstructive CRDs;

asthma and COPD[3]. The details of these costing and cohort studies are in chapters three and four of this thesis. Finally, I developed and used a Markov model for COPD and asthma using empirical data from Malawi, to evaluate the costs, effects, and cost-effectiveness of selected possible interventions for Malawian adults; details of which are reported in chapters four and five of this thesis.

This chapter summarises the main findings from the studies conducted in this PhD, reports the policy and decision-making implications and recommendations, and suggests further research that could enhance CRD care that is provided in Malawi and similar settings.

6.1 Estimating the health burden of airflow obstruction in Malawi.

The cohort study presented in chapters two and three aimed to assess the health burden of airflow obstruction in Malawi by conducting a longitudinal study and reporting on a utility-based health-related quality of life (HRQoL) in relation to lung function decline and chronic respiratory disease in sub-Saharan Africa.

In a five-year follow-up study as part of the Chikwawa lung health cohort[12], we recruited adults from villages in Chikwawa, rural Malawi. We measured their lung function by spirometry, quantified their respiratory symptoms and HRQoL, and used linear mixed-effects models to analyse the lung function and HRQoL scores.

In this study, we report an adjusted annual rate of decline of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) decline of (95% CI: 49·0, 57·8) and 45·2 ml/year (39·2, 50·5), respectively. The FEV_1 annual rate of decline reported is like that in smokers of ≥ 15 cigarettes/day in HICs[13,14] in keeping with previous studies from Malawi[10]. This decline was driven by factors other than smoking unlike in high income countries (HICs)[15], since Malawi has low levels of smoking[10,16,17]. The cause(s) of the relatively rapid rate of FEV_1 decline in this study is unclear but may be a result of frequent pulmonary infections consequent upon

genetic factors and/or dietary factors. The prevalence of chronic obstructive pulmonary disease nearly doubled from 9·5% (7·6%, 11·6%) in 2014 to 17·5% (15·3%, 19·9%) in 2019. Importantly, reduced FEV_1 (but not rate of decline) was associated with diagnosed asthma, previous TB, and spirometry consistent with COPD, asthma, and restriction, suggesting that most of the differences in lung function occurred prior to cohort set up and were not a consequence of differential rates of FEV_1 decline during follow-up. This finding is consistent with reports from cohort studies in HICs that reductions in FEV_1 in later adult life observed in COPD and asthma are largely a consequence of the tracking of suboptimal lung function from childhood into adulthood[18–20].

The second main finding from this study was declining lung functions and symptoms of dyspnoea, wheeze, and cough, previously diagnosed TB are adversely and independently associated with reductions in HRQoL that were clinically significant being greater than the minimally important difference (MID) of (0·033, 95% CI: 0·029–0·037)) and in people with COPD (MID: 0·011, (SD 0·09))[21]. This is the first longitudinal study of HRQoL in relation to ventilatory function and chronic respiratory disease in sub-Saharan Africa. Previous cross-sectional studies on LMICs have found respiratory HRQoL (St Georges Respiratory Questionnaire) is adversely associated with dyspnoea[22] and reduced HRQoL (SF-12) is associated with chronic bronchitis symptoms[23].

In summary in this study of adults living in rural Malawi: 1) Annual rate of lung function decline is similar to that in smokers of ≥ 15 cigarettes/day in HICs; 2) Reduced lung function (but not rate of decline) was associated with previous TB, asthma, COPD and restriction, suggesting that most of the differences in lung function occurred before the cohort's Inception and were not a consequence of differential rates of lung decline during follow-up; 3) The prevalence of COPD, one of the commonest obstructive CRDs, has increased by 1–2% a year and is

associated with the reduced lung function, combined with lung function deficits present before recruitment; and, 4) Respiratory symptom burden and sub-optimal lung function are independently associated with reduced HRQoL of magnitude greater than the minimal important difference.

6.2 Estimating the current economic cost of chronic obstructive pulmonary disease and asthma in Malawi

Chapter four of this thesis aimed to estimate the current economic burden from health provider and patient perspectives, of airflow obstruction in Malawi by calculating health costs and the unmet need for COPD and asthma care (the most prevalent chronic respiratory diseases (CRDs)[3]) in the Malawian health system through measuring health service attendance and resource use, and associated treatment cost in population cohorts, as well as the additional out-of-pocket (OOP) cost and productivity losses per patient.

In this economic study, patient health resource use and costs were obtained from three adult population cohort studies in southern Malawi[8,12,24], health provider input and costs were obtained from a micro-costing study in addition to data on health resource use by adults from the previous studies[12,24], and a bespoke costing study to collect data on staffing and time spent reviewing patients with respiratory diseases[12] at the chest clinic of Queen Elizabeth Central Hospital(QECH), one of the largest referral health facilities in Malawi. The chest clinic at QECH is the regional free-to-access specialist outpatient clinic for all patients with respiratory complaints. The costs estimated are generalisable to a Malawian patient with COPD or asthma as they are likely to get their care from QECH as it is a regional hospital that is adequately staffed and stocked with a chest clinic compared to their local health centre thus if they have the ability, they will seek care from QECH.

By conducting a non-parametric bootstrap analysis[25] of 100,000 resamples with replacement of the original reported participant data from our cohort studies[8,12], estimates of the confidence intervals of the calculated annual per capita costs of asthma (wheeze in last year) and COPD (typical lung function) were obtained. An ingredient approach was used to estimate resource use and costs and reported in 2020 US$ while adjusting for inflation with a one year time horizon.

This study found the asthma costs are US$108 (bootstrap 95% CI: 87–132) per year while COPD costs are US$143 (bootstrap 95% CI: 124–165) per year. These costs are comparable to other LMIC settings[24,26], but they are significantly lower than the costs incurred in HIC settings[27], in part anecdotally due to the associated lower productivity losses estimated in LMICs. COPD and asthma care costs are driven by hospital in- and out-patient episodes to treat acute/sub-acute exacerbations. In both COPD and asthma moderate/severe disease severity is associated with at least a tripling of medication costs compared to mild disease severity. Based on the estimated costs, the per capita cost of universal coverage for those with asthma or COPD who do not currently engage with the health system is likely to exceed the average per-capita health expenditure in Malawi of US$35 per year[28].

In this study, diagnosis of CRDs remained low resulting in 74.1% of the participants with asthma and 77.3% of the participants with COPD having an unmet need after accessing a health facility. This could be due to the lack of essential CRD interventions as a previous study had reported that beclomethasone inhalers, prednisolone tablets, hydrocortisone injections and oxygen were only available in 6%, 43%, 22% and 16% respectively in health facilities in Malawi[29], in keeping with other studies from sub-Saharan Africa[30].

In summary, in this costing study of COPD and asthma care in Malawian health facilities: 1) the estimated costs are substantial ranging from one and half time to about five times the

average total per-capita health expenditure in Malawi; 2) the major contributors of costs are in and out-patient hospital episodes to treat acute/sub-acute exacerbations; 3) there was evidence of substantial undertreatment for asthma and COPD.

6.3 Estimating the future economic cost, effects, and cost-effectiveness of selected key interventions for adults with chronic obstructive pulmonary disease and asthma in Malawi.

The decision analytic model presented in chapters five aimed to estimate the future cost and cost-effectiveness of selected interventions for adults with airflow obstruction in Malawi by developing a Markov model for COPD and asthma using empirical data from Malawi, to evaluate the costs and effects of possible interventions that could be implemented in the Malawian health system.

In the asthma and COPD model described in this thesis, data on prevalence, lung function decline, exacerbations, health-related quality-of-life, health resource use and costs were combined into a probabilistic dynamic prevalence model describing the lifetime natural history of patients with COPD or asthma in Malawi and summarized by health-adjusted life expectancy and lifetime health costs. The model was used to estimate the cost-effectiveness of widespread use of a self-management plan that includes the keeping of anticipatory 'emergency packs' of antibiotics and corticosteroids at home that are self-administered in the early stages of exacerbation[31] compared with usual care for COPD and widespread administration of inhaled beclomethasone (100ug/puff) and salbutamol (100ug/puff)[32,33] compared with usual care for asthma.

The study found that, the COPD intervention was less costly and more effective than usual care in the people with mild COPD while the ICERs were US$ 72, US$102, and US$ 242 in people with mild asthma, moderate/severe asthma, and moderate/severe COPD respectively.

The asthma intervention resulted in a life-years gain of 1.62 years and 1.29 years in the patients with mild asthma and moderate/severe asthma respectively while the COPD intervention resulted in a life-years gain of 3.49 years and 3.90 years in patients with mild COPD and moderate/severe COPD respectively. The univariate sensitivity analysis found that the cost of managing moderate/severe COPD is associated with the highest impact on the uncertainty in the model. We found an 80% probability of being cost-effective at a willingness-to-pay threshold of about US$ 110 per QALY for the COPD intervention and US$ 400 per QALY for the asthma intervention. While both interventions are lower than the US$ 500 than we found best reflected the GDP per capita of Malawi[34], both interventions resulted in ICERs that would be out of reach for the Malawian health system as presently the average per-capita health expenditure in Malawi of US$ 35 per year[28].[28]

To get better and more accurate data on the effectiveness of asthma and COPD interventions, lung health randomised control trials including health economic outcomes will need to be conducted in LMICs settings. In addition, to get better estimates for the mortality transition probabilities and health states, data from national registries will be vital. Although we validated our estimated mortality transition probabilities with published studies[35–38], our study estimated effectiveness of asthma and COPD interventions is likely to different from outcomes that could result from a well conducted RCT in Malawi. We used intervention efficacy outcome data from published systematic and Cochrane reviews[31–33] making our findings internally valid, but a pragmatic trial conducted in Malawi would provide Malawi-specific effectiveness outcomes that would be invaluable and strengthen the external validity of our findings.

In summary, in this cost-effectiveness study of COPD and asthma interventions in the Malawian situation: 1) the COPD intervention dominated usual care in the people with mild

COPD while the ICERs were between US$ 72 and US$ 242 in the other disease states in the deterministic analysis; 2) life-years gain of between 1.29 years 3.90 years in patients with COPD or asthma; 3) the univariate sensitivity analysis found that the cost of managing moderate/severe COPD is associated with the highest impact on the uncertainty in the model; 4) We recommend that the COPD be implemented as it results in cost-savings in the long term, dominates usual care in patients with mild COPD and in the probabilistic analysis results in lower ICER outcomes for all patients with COPD; and 5) We recommend that a budget impact analysis to be done to find ways to implement the asthma intervention.

6.4 What does the future hold?

This PhD set out to estimate the health burden economic cost of airflow obstruction from a societal perspective and to identify efficient interventions to address the estimated burden. The unit cost estimates, and economic modelling methods reported should support prioritisation and provision of effective interventions, the design of crucial CRD health services and budgeting for lung programmes. Dissemination activities should provide an opportunity to get further input and validation from policy makers in Malawi.

While the work in this PhD estimated a relatively rapid rate of FEV_1 decline, it was unclear what caused the rate of decline. Future studies of early life cohort studies investigating the risk factors of pulmonary infections consequent upon genetic factors and/or dietary factors could provide some answers as to what causes the rate of decline in Malawi and similar population. While the CAPS cluster randomized trial[39] found no evidence that a cleaner burning biomass-fuelled intervention reduced the risk for pneumonia, it did not exclude the role of biomass and other environmental exposures on the rapid decline in lung function. Population-based early life cohort studies could investigate the risk factors of pulmonary infections and the rapid lung function decline.

To get better and more accurate data on the effectiveness of asthma and COPD interventions, lung health randomised control trials including health economic outcomes will need to be conducted in LMICs settings. These trials coupled with patient-level simulation will provide better costs and effects estimates for each unique patient in the Malawian situation.

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7 Appendices

7.1 Appendix A: Ethical approval

7.1.1 Appendix A1: COMREC ethical approval

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.03/19/2617 - Assessing the societal burden of airflow obstruction and modelling the potential impact of leading interventions amongst adults in Malawi(ALDM Study) version 2.0 by Mr Martin W. Njoroge

On 14-Apr-19

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 some of which are indicated on the next page for your study

14-Apr-19

Dr. YB. Mlombe - Chairperson (COMREC)

Date

REQUIREMENTS FOR YOUR COMREC APPROVED RESEARCH PROTOCOL

1. Pay the research overhead fees as required by the College of Medicine for all approved studies (except undergraduate 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 end of study (close-out) 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 13-Apr-20. 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.

7.1.2 Appendix A2: LSTM ethical approval

Mr. Martin W. Njoroge
Liverpool School of Tropical Medicine
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Liverpool
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Wednesday, 24 April 2019

Dear Mr Njoroge,

Research Protocol (19-005) Assessing the societal burden of airflow obstruction and modelling the potential impact of leading interventions amongst adults in Malawi.

Thank you for your letter 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 23 April 2022. 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 Martyn Stewart
Acting Chair
Research Ethics Committee

7.2 Appendix B: Data collection tools in English and Chichewa

7.2.1 Appendix B1: Spirometry questionnaire

Identification
Site
Fieldworker number
Participant number
1. Pulse (bpm)
2.1. Systolic blood pressure (mmHg)
2.2. Diastolic blood pressure (mmHg)
3. Height (cm)
4. Weight (kg)
5.1. Hip circumference 1st measurement (cm)
5.2. Hip circumference 2nd measurement (cm)
6.1. Waist circumference 1st measurement (cm)
6.2. Waist circumference 2nd measurement (cm)
7. Ulna length (cm)
8. Fibula length (cm)
9.1. Neck circumference 1st measurement (cm)
9.2. Neck circumference 2nd measurement (cm)
10. Comments
11. In the past three months have you had any surgery on your chest or abdomen?
12. Have you had a heart attack within the past three months?
13. Do you have a detached retina or have you had eye surgery within the past three months?
14. Have you been hospitalized for any other heart problem within the past month?
15. Are you in the last trimester of pregnancy?
16. Are you currently taking medication for tuberculosis?
17. Is there some other reason why this participant should not perform the spirometry manoeuvre?
DO NOT PERFORM SPIROMETRY!
18. Have you had a respiratory infection (cold) in the last three weeks?
19. Have you taken any medications for breathing in the last 24 hours?
Recent medications
20. Record name/type of medication(s) used:
20.1. Did participant use a short acting beta agonist (e.g., albuterol, salbutamol) or anticholinergic inhaler (e.g., atrovent, iprtropium), either alone or in combination with some other product, in the last six hours?
20.2. Did participant use a long acting beta agonist (e.g.Serevent, Advair, Formoterol, Symbicort) or oral beta 2 agonist (e.g., salbutamol tablets), either alone or in combination with some other product, in the last 12 hours?
20.3. Did participant use an oral theophyllin/ long acting anticholinergic (e.g., spiriva, tiotropium), either alone or in combination with some other product, in the last 24 hours?
21. Have you smoked in the last 30 days?

21.1. When did you last smoke?
22.1. Acceptable pre-bronchodilator test completed?
22.2. Acceptable post-bronchodilator test completed?
23. Why were you unable to obtain satisfactory spirometry?
24. Were any adverse events related to the spirometry manoeuvre observed by the evaluator?
25. Was this a major event (was the participant hospitalised or did the participant die)?
26. Please briefly describe event:
27. If the participant had a condition that would affect the result of their spirometry test (e.g., kyphosis, missing limbs, etc.) note that condition here.

7.2.2 Appendix B2: Core questionnaire

Identification
Site
Fieldworker number
Participant number
1. What is the participant's sex?
2. What is your date of birth?
Education
3. What is the _highest level_ of schooling your _mother_ has completed?
Household assets
4.1. Please tell me whether this household or any person who lives in the household has/owns the following items:
4.1.1. Electricity?
4.1.2. Flush toilet?
4.1.3. Fixed telephone?
4.1.4. Cell telephone?
4.1.5. Television?
4.1.6. Radio?
4.1.7. Refrigerator?
4.1.8. Car?
4.1.9. Moped/scooter/motorcycle?
4.1.10. Washing machine?
4.1.11. Own their own home?
4.1.12. Indoor bath or shower?
4.1.13. Indoor tap?
4.1.14. Outdoor tap of their own?
4.1.15. Country to specify
4.1.16. Country to specify
4.2. When you were _5 years old_ did any person who lived in your household have/own the following items:
4.2.1. Electricity?
4.2.2. Flush toilet?
4.2.3. Fixed telephone?
4.2.4. Television?
4.2.5. Radio?
4.2.6. Refrigerator?
4.2.7. Car?
4.2.8. Moped/scooter/motorcycle?

4.2.9. Washing machine?
4.2.10. Own their own home?
4.2.11. Indoor bath or shower?
4.2.12. Indoor tap?
4.2.13. Outdoor tap of their own?
5. In the last year did you or any person who lives in the household ever go hungry for lack of money?
5.1. How often did you or any person who lives in the household ever go hungry for lack of money?
6. How many _people_ live in your house with you? (including you)
7. How many _rooms_ are there in your house? (excluding kitchen and bathroom/s)
Respiratory symptoms
These questions pertain mainly to your __chest__. Please answer yes or no if possible. If you are in doubt about whether your answer is yes or no, please answer no.
8. Do you _usually_ cough when you don't have a cold?
8.1. Are there _months_ in which you cough on _most days_?
8.2. Do you cough on _most days_ for as much as _three months each year_?
8.3. For how _many years_ have you had this cough?
9. Do you _usually_ bring up _phlegm_ from your _chest_, or do you usually have phlegm in your chest that is difficult to bring up when you don't have a cold?
9.1. Are there _months_ in which you have this phlegm on most days?
9.2. Do you bring up this phlegm on _most days_ for as much as three months each year?
9.3. For how many _years_ have you had this phlegm?
9.4. Is the phlegm worse when you lie in certain positions (on one side or the other)?
10. Have you had _wheezing_ or _whistling_ in your chest at any time in the _last 12 months_?
10.1. In the _last 12 months_, have you had this wheezing or whistling _only_ when you have a cold?
10.2. In the _last 12 months_, have you ever had an attack of wheezing or whistling that has made you feel _short of breath_?
11. Are you _unable_ to walk due to a condition _other than_ shortness of breath?
11.1. Nature of condition(s):
Exertional Dyspnoea
12. Are you troubled by shortness of breath when _hurrying on the level_ or _walking up a slight hill_?
12.1. Do you have to walk slower than people of _your age_ on _level ground because of shortness of breath?
12.2. Do you ever have to _stop for breath_ when walking at your _own pace_ on _level ground_?
12.3. Do you ever have to stop for breath after _walking about 100 yards_ (or after a few minutes) on _level ground_?
12.4. Are you too short of breath to leave the house or short of breath on dressing or undressing?
Respiratory diagnoses

13. Has a _doctor or other health care provider_ ever told you that you have emphysema?
14. Has a _doctor or other health care provider_ ever told you that you have asthma, asthmatic bronchitis or allergic bronchitis?
14.1. Do you _still_ have asthma, asthmatic bronchitis or allergic bronchitis?
15. Has a _doctor or other health care provider_ ever told you that you have chronic bronchitis?
15.1. Do you _still_ have chronic bronchitis?
16. Has a _doctor or other health care provider_ ever told you that you have chronic obstructive pulmonary disease (COPD)?
17. In the past _12 months_, have you taken any medications for your breathing (including medications for nasal congestion)?
Medications
17.1. How many medicines have you taken for your breathing (including medications for nasal congestion) in the past 12 months?
Medications: Details
17.2. Medication Name(s):
17.2.1. Formulation:
17.2.2. Is the medicine taken on most days, or just when you have symptoms, or both?
17.2.3. When you are taking the medication, how many _days_ a week do you take it?
17.2.4. When you are taking the medication, how many _months_ in the past 12 months have you taken it?
17.3. Please tell me about any other products that you take or things you do to _help_ your breathing that you have not already told me about.
Spirometry and breathing problems
18. Has a _doctor or other health care provider_ ever had you blow into a machine or device in order to measure your lungs (i.e., a spirometer or peakflow meter)?
18.1. Have you used such a machine in the past _12 months_?
19. Have you ever had a period when you had breathing problems that got so bad that they interfered with your usual daily activities or caused you to miss work?
19.1. How many such episodes have you had in the past 12 months?
19.2. For how many of these episodes did you need to see a doctor or other health care provider in the past 12 months?
19.3. For how many of these episodes were you hospitalized overnight in the past 12 months?
19.3.1. All together, for how many total _days_ were you hospitalized overnight for breathing problems in the past 12 months?
Sleep
20. How many hours of sleep do you estimate that you get on average each night?
21. Do you snore?
21.1. Your snoring is:

21.2. How often do you snore?
21.3. Has your snoring ever bothered other people?
22. Has anyone noticed that you quit breathing during your sleep?
23. Do you gasp for air or choke while sleeping?
23.1. In the last month on how many nights per week did you gasp for air or choke while sleeping?
24. In the past month, how often have you felt _sleepy during the day_?
25.1. How likely are you to doze off while sitting in a _public place_ (for instance in a theatre or meeting)?
25.2. How likely are you to doze off while sitting down and _talking to someone_?
25.3. How likely were you to doze off while sitting _quietly_ after a meal without alcohol?
26. In the past month, how often have you had _heartburn after lying down_?
27. In the past month, how often have you _sweated or perspired excessively_ during the night?
28. During your waking time, how often do you feel tired, fatigued or not up to par?
29. In the past three months, how often have you woken up at least 30 minutes earlier in the morning and been unable to get back to sleep?
30. In the past three months, how often have you woken from sleep _several_ times during the night?
31. In the past three months, how often have you had difficulties _falling asleep_ (taken more than 30 minutes)?
Smoking
31. Now I am going to ask you about smoking. First I will ask about cigarettes, including hand rolled cigarettes, and then I will ask about other items that are smoked.
31.1. Have you _ever_ smoked __cigarettes__?
31.1.1. How _old_ were you when you first started regular cigarette smoking?
31.1.2. Have you _stopped_ smoking?
31.1.2.1. How _old_ were you when you last _stopped_?
31.1.3. On _average_ over the entire time that you smoke(d), how many cigarettes per day/week do (did) you smoke?
31.1.3.1. cigarettes/day
31.1.3.2. cigarettes/week
31.1.4. On average over the entire time that you smoke(d), do (did) you primarily smoke manufactured _or_ hand-rolled cigarettes?
31.2. Have you _ever_ smoked __beedi__?
31.2.1. How _old_ were you when you first started regular beedi smoking?
31.2.2. Have you ever _stopped_ smoking beedi?

31.2.2.1. How _old_ were you when you last stopped?
31.2.3. On _average_ over the entire time that you smoke(d), about how many beedi per day/per week do (did) you smoke?
31.2.3.1. beedi/day
31.2.3.2. beedi/week
31.3. Have you _ever_ smoked __kreteks__?
31.3.1. How _old_ were you when you first started regular kreteks smoking?
31.3.2. Have you ever _stopped_ smoking kreteks?
31.3.2.1. How _old_ were you when you last stopped?
31.3.3. On _average_ over the entire time that you smoke(d), about how many kreteks per day/per week do (did) you smoke?
31.3.3.1. kreteks/day
31.3.3.2. kreteks/week
31.4. Have you _ever_ smoked __pipes of tobacco__?
31.4.1. How _old_ were you when you first started regular pipe smoking?
31.4.2. Have you ever _stopped_ smoking tobacco pipes?
31.4.2.1. How _old_ were you when you last stopped?
31.4.3. On _average_ over the entire time that you smoke(d), about how many grams per day/per week do (did) you smoke?
31.4.3.1. grams/day
31.4.3.2. grams/week
31.5. Have you _ever_ smoked __cigars, cheroots, or cigarillos__?
31.5.1. How _old_ were you when you first started regular cigar/cheroot/cigarillo smoking?
31.5.2. Have you _stopped_ smoking cigars, cheroots, or cigarillos?
31.5.2.1. How _old_ were you when you last stopped smoking a cigar, cheroot or cigarillo?
31.5.3. On _average_ over the entire time that you smoke(d), about how many cigar/cheroot/cigarillo per day/per week do (did) you smoke?
31.5.3.1. cigars, etc/day
31.5.3.2. cigars, etc/week

31.6. Have you _ever_ smoked a __water pipe__?
31.6.1. How _old_ were you when you first started regular water pipe smoking?
31.6.2. Have you stopped_ smoking water pipe?
31.6.2.1. How _old_ were you when you last stopped smoking a water pipe?
31.6.3. On _average_ over the entire time that you smoke(d), about how many water pipes per day/per week do (did) you smoke?
31.6.3.1. water pipe/day
31.6.3.2. water pipe/week
31.7. Have you _ever_ smoked __cannabis__?
31.7.1. How _old_ were you when you first started regular cannabis smoking?
31.7.2. Have you _stopped_ smoking cannabis?
31.7.2.1. How _old_ were you when you first started cannabis smoking?
31.7.3. On _average_ over the entire time that you smoke(d), about how many joints/splifs/pipes of cannabis per day/per week do (did) you smoke?
31.7.3.1. joints/day
31.7.3.2. joints/week
31.8. Have you _ever_ vaped/smoked __e-cigarettes__?
31.8.1. How _old_ were you when you first started regular vaping/e-cigarette smoking?
31.8.2. Have you ever _stopped_ vaping/smoking e-cigarettes?
31.8.2.1. How _old_ were you when you last stopped?
31.8.3. On _average_ over the entire time that you vaped/smoke(d), about how many e-cigarettes cartridges per day/per week do (did) you use?
31.8.3.1. e-cigarette cartridges/day
31.8.3.2. e-cigarette cartridges/week
31.8.4. Have you ever vaped/smoked e-cigarettes with aroma(s)?
31.9. Have you ever smoked or inhaled any _other_ substance? (e.g., local, recreational smoked substances)
31.9.1. specify type:
31.9.2. specify unit. e.g., pipes, joints

31.9.3. How old_ were you when you first started regularly smoking this?
31.9.4. On _average_ over the entire time that you smoke(d), about how many units per day/per week do (did) you smoke?
31.9.4.1. units/day
31.9.4.2. units/week
32. Are you _currently_ smoking anything?
33. How soon after you wake up do you smoke your first cigarette/e-cigarette/beedi/kretek/pipe of tobacco/cigar, cheroot, or cigarillo/water pipe?
34. Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., church, library, cinema, restaurant)?
35. Which cigarette/e-cigarette/beedi/kretek/pipe of tobacco/cigar, cheroot, or cigarillo/water pipe would you be the most unwilling to give up?
36. Do you smoke more frequently during the first hours after waking than during the rest of the day?
37. Do you smoke if you are so ill that you are in bed most of the day?
38. In the last year, how many times have you quit smoking for at least 24 hours?
38.1. Are you seriously thinking of quitting smoking?
38.2. Has a doctor or other health care provider ever _advised_ you to quit smoking?
38.3. Have you received medical advice to stop smoking within the past _12 months_?
38.4. Have you used any medication (prescription or non-prescription), including a nicotine patch, to help you stop smoking?
38.4.1. What kind of _medication_ did you take to help you _stop_ smoking?
38.4.2. Have you used or done _anything else_ to help you stop smoking?
38.4.2.1. What did you do?
39. Has anyone living in your home (besides yourself) smoked a cigarette, pipe or cigar in your home during the past _two weeks_?
39.1. Not counting yourself, how many people in your _household_ smoke regularly?
39.2. Do people smoke regularly in the room where you _work_?
39.3. How many _hours_ per day, are you exposed to other people's tobacco smoke in the following locations?
39.3.1. In the home?
39.3.2. In the workplace?
39.3.3. In bars, restaurants, cinemas or similar social settings?
39.3.4. Elsewhere?
Intro: The following questions refer _only_ to cigarettes and tobacco
39.4. Based on what you know or believe, does smoking tobacco _cause_ serious illness?
39.5. Based on what you know _or_ believe, does smoking tobacco cause the following…
39.5.1. Stroke (blood clots in the brain that may cause paralysis)
39.5.2. Heart attack
39.5.3. Lung cancer
39.5.4. Chronic bronchitis

39.5.5. Emphysema/COPD
40. Have you ever worked for a year or more in a dusty job?
40.1. For how many years have you worked in dusty jobs?
41. Has a doctor or other health care provider ever told you that you had:
41.1. Heart disease
41.1.1. Heart failure
41.2. Hypertension
41.3. Diabetes
41.4. Lung cancer
41.5. Stroke
Tuberculosis
42. Have you _ever_ been diagnosed with __tuberculosis__?
42.1. How many times have you been treated for tuberculosis?
Please answer these questions for the __most recent__ episode.
42.2. When were you last diagnosed as having tuberculosis? (year)
42.3. What part of the body did the tuberculosis affect?
42.4. Were the doctors/clinic _sure_ that you had tuberculosis?
42.4.1. Which tests showed that you had tuberculosis?
42.5. Did you ever stay in hospital for treatment of tuberculosis?
42.5.1. How long for were you in the hospital (sleeping in the hospital)?
42.6. Where did you get your pills or injections for tuberculosis (which clinic)?
42.7. How long _(in months)_ did you take treatment for?
42.8. Did you finish the treatment?
42.8.1. Why did you _not_ complete the treatment?
42.8.2. Did you feel partly or completely well again (better) after ending treatment?
42.8.3. Did the clinic doctor say you were cured?
42.8.4. Did you _stop_ attending the clinic before the treatment was meant to stop?
Other
43. Have you ever had an operation on your chest in which a part of your lung was _removed_?
44. In the past 12 months did you get a flu shot?
45. Has a doctor or other health care _professional_ told your father, mother, sister or brother that they had a diagnosis of emphysema, chronic bronchitis or COPD?
Quality of Life
The following questions ask for your views about your health—how you feel and how well you are able to do your usual activities. There are no right or wrong answers; please choose the answer that best fits your life right now.
46. In general, would you say your health is: _(Check one)_
47. Does _your health __now__ limit_ you in these activities? If so, how much?
47.1. _Moderate activities_, such as moving a table pushing a vacuum cleaner, bowling or playing golf.

47.2. Climbing _several_ flights of stairs.
48. During _the past 4 weeks_, have you had any of the following problems with your work or other regular daily activities _as a result of your physical health_?
48.1. _Accomplished less_ than you would like.
48.2. Were limited in the _kind_ of work or other activities .
49. During the _past 4 weeks_ have you had any of the following problems with your work or other regular daily activities _as a result of any emotional problems_ (such as feeling depressed or anxious)?
49.1. _Accomplished less_ than you would like.
49.2. Didn't do work or other activities as _carefully_ as usual.
50. During the _past 4 weeks_, how much did pain interfere with your normal work (including both work outside the home and housework)?
These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.
51. How much of the time during the _past 4 weeks_…
51.1. Have you felt calm and peaceful?
51.2. Did you have a lot of energy?
51.3. Have you felt downhearted and blue?
51.4. Have you felt tired?
52. During the _past 4 weeks_, how much of the time has your _physical health or emotional problems_ interfered with your social activities (like visiting friends, relatives, etc.)?
52.1. Compared to one year ago, how would you rate your _physical_ health in general now?
52.2. Compared to one year ago, how would you rate your _emotional_ problems (such as feeling anxious, depressed or irritable) now?
Work
The next questions ask about work and about times when you may have missed work due to _health problems_.
53. At any time in the past 12 months, did you work for income?
Paid Employment
53.1. During how many of the past 12 months did you work for income?
53.2. During the months that you worked, how many _days per week_ did you work for income?
53.3. What is the usual number of _hours per day_ you work for income?
53.4. During the past 12 months, did health problems ever stopped you from working for income?
53.4.1. During the past 12 months, how many _total days_ were you unable to work for income due to your health problems?
53.4.2. During the past 12 months, how many _total days_ were you unable to work for income specifically due to breathing problems?
53.5. During the past 12 months, did you not work for income mainly due to _breathing_ problems?
53.6. During the past 12 months, did you not work for income because you were a full-time homemaker or caregiver?

53.7. During the past 12 months, did health problems prevent you from participating in one or more non-work related activities?
53.7.1. During the past 12 months, how many total days did you not participate in non-work related activities due to your health problems?
53.7.2. During the past 12 months, how many _total days_ did you not participate in non-work related activities specifically due to breathing problems?
53.7.3. During the past 12 months, did health problems stop you from performing your usual homemaking/caregiving tasks?
53.7.3.1. During the past 12 months, how many total days were you unable to perform your homemaking/caregiving tasks due to your health problems?
53.7.3.2. During the past 12 months, how many total days were you unable to perform your homemaking/caregiving tasks specifically due to breathing problems?
Physical activity
Next, I am going to ask you about the time you spend doing different types of physical activity in a typical week. Please answer these questions even if you do not consider yourself to be a physically active person.
Think about all the _vigorous_ activities that you did in the last 7 days. Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.
54. During the _last 7 days_, on how many days did you do _vigorous_ physical activities like heavy lifting, digging, aerobics, or fast bicycling?
54.1. How much time (hours) did you usually spend doing vigorous physical activities on one of those days?
Think about all the _moderate_ activities that you did in the last 7 days. Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.
55. During the _last 7 days_, on how many days did you do _moderate_ physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.
55.1. How much time (hours) did you usually spend doing moderate physical activities on one of those days?
Think about the time you spent _walking_ in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.
56. During the _last 7 days_, on how many days did you _walk_ for at least 10 minutes at a time?
56.1. How much time (hours) did you usually spend walking on one of those days?
The last question is about the time you spent _sitting_ on weekdays during the last 7 days. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.
57. During the _last 7 days_, how much time (hours) did you spend _sitting_ on a week day?

7.2.3 Appendix B3: Verbal autopsy questionnaire

Identification
Site
Fieldworker number
Participant number
Status of participant
1. Can the participant be contacted?
1.1. Why can't the participant be contacted?
1.2. When was this person last heard from?
Cause of death
2. What is the relation between the deceased and the informant?
3. Is there a death certificate?
Death Certificate
3.1. What is the date of death on the certificate?
3.2. Is the ICD code available
ICD Codes
3.2.1.1. Record the immediate cause of death from the certificate.
3.2.1.2. Record the first underlying cause of death from the certificate.
3.2.1.3. Record the second underlying cause of death from the certificate.
3.2.1.4. Record the first contributing cause of death from the certificate.
3.2.1.5. Record the second contributing cause(s) of death from the certificate.
Uncoded causes of death
3.2.2.1. Record the immediate cause of death from the certificate.
3.2.2.2. Record the first underlying cause of death from the certificate.
3.2.2.3. Record the second underlying cause of death from the certificate.
3.2.2.4. Record the third underlying cause of death from the certificate.
3.2.2.5. Record the contributing cause(s) of death from the certificate.
Verbal Autopsy
****SECTION 1: INJURIES AND ACCIDENT****
4. Did [*participant's name*] suffer from an injury or accident that led to his/her death?
4.1. What kind of injury or accident did [*participant's name*] suffer from?
4.1.1. Specify other:
4.2. Was the injury or accident self-inflicted?
4.3. Was the injury or accident intentionally inflicted by someone else?
****SECTION 2: HISTORY OF CHRONIC CONDITIONS OF THE DECEASED****

5. Was [*participant's name*] ever told by a health professional that he or she ever suffered from one of the following?
5.1. Asthma
5.2. Cancer
5.3. COPD (Chronic Obstructive Pulmonary Disease)
5.4. Diabetes
5.5. Epilepsy
5.6. Heart Disease
5.7. Tuberculosis
5.8. Stroke
5.9. AIDS
****SECTION 3: SYMPTOM CHECKLIST****
These questions pertain mainly to the 12 months prior to the death of [*participant's name*]
6.1. Did [*participant's name*] have a fever?
6.1.1. How severe was the fever?
6.1.2. What was the pattern of the fever?
6.2. Did [*participant's name*] have a rash?
6.2.1. Where was the rash located?
6.3. Did [*participant's name*] have sores?
6.3.1. Did the sores have clear fluid or pus?
6.4. Did [*participant's name*] have an ulcer (pit) on the foot?
6.4.1. Did the ulcer ooze pus?
6.4.2. For how many days did the ulcer ooze pus?
6.5. Did [*participant's name*] experience “pins and needles” in their feet?
6.6. Did [*participant's name*] have blue lips?
6.7. Had [*participant's name*] lost weight in the three months prior to death?
6.7.1. How substantial was the loss of weight?
6.8. Did [*participant's name*] look pale?
6.9. Did [*participant's name*] have yellow discoloration of the eyes?
6.9.1. For how long did [*participant's name*] have the yellow discoloration?
6.9.1.1. Days:
6.9.1.2. Months:
6.10. Did [*participant's name*] have ankle swelling?
6.10.1. For how long did [*participant's name*] have ankle swelling?
6.10.1.1. Days:
6.10.1.2. Months:
6.11. Did [*participant's name*] have puffiness of the face?
6.11.1. For how long did [*participant's name*] have puffiness of the face?
6.11.1.1. Days:
6.11.1.2. Months:
6.12. Did [*participant's name*] have general puffiness all over his/her body?

6.12.1. For how long did [*participant's name*] have puffiness all over his/her body?
6.12.1.1. Days:
6.12.1.2. Months:
6.13.1. Did [*participant's name*] have a lump in the neck?
6.13.2. Did [*participant's name*] have a lump in the armpit?
6.13.3. Did [*participant's name*] have a lump in the groin?
6.14. Did [*participant's name*] have a cough?
6.14.1. For how long did [*participant's name*] have a cough?
6.14.1.1. Days:
6.14.1.2. Months:
6.14.2. Did the cough produce sputum?
6.15. Did [*participant's name*] cough blood?
6.16. Did [*participant's name*] have difficulty breathing?
6.16.1. For how long did [*participant's name*] have difficulty breathing?
6.16.1.1. Days:
6.16.1.2. Months:
6.16.2. Was the difficulty continuous or on and off?
6.16.3. In what position did the difficulty get worse?
6.17. Did [*participant's name*] have fast breathing?
6.17.1. For how long did [*participant's name*] have fast breathing?
6.17.1.1. Days:
6.17.1.2. Months:
6.18. Did [*participant's name*] wheeze?
6.19. Did [*participant's name*] experience pain in the chest in the month preceding death?
6.19.1. How long did the pain last?
6.19.2. Was the pain during physical activity?
6.19.3. Where was the pain located?
6.20. Did [*participant's name*] have more frequent loose or liquid stools than usual?
6.20.1. Was there blood in the stool?
6.20.2. Was there blood in the stool up until death?
6.21. Did [*participant's name*] stop urinating?
6.22. Did [*participant's name*] vomit in the week preceding the death?
6.22.1. Was there blood in the vomit?
6.22.2. Was the vomit black?
6.23. Did [*participant's name*] have difficulty swallowing?
6.23.1. For how long before death did [*participant's name*] have difficulty swallowing?
6.23.1.1. Days:
6.23.1.2. Months:
6.23.2. Was the difficulty with swallowing with solids, liquids, or both?

6.23.3. Did [*participant's name*] have pain upon swallowing?
6.24. Did [*participant's name*] have belly pain?
6.24.1. For how long before death did [*participant's name*] have belly pain?
6.24.1.1. Hours:
6.24.1.2. Days:
6.24.1.3. Months:
6.24.2. Was the pain in the upper or lower belly?
6.25.Did [*participant's name*] have a more than usual protruding belly?
6.25.1. For how long before death did [*participant's name*] have a protruding belly?
6.25.1.1. Days:
6.25.1.2. Months:
6.25.2. How rapidly did [*participant's name*] develop the protruding belly?
6.26. Did [*participant's name*] have any mass in the belly?
6.26.1. For how long before death did [*participant's name*] have a mass in the belly?
6.26.1.1. Days:
6.26.1.2. Months:
6.27. Did [*participant's name*] have a stiff neck?
6.27.1. For how long before death did [*participant's name*] have stiff neck?
6.27.1.1. Days:
6.27.1.2. Months:
6.28. Did [*participant's name*] experience a period of loss of consciousness?
6.28.1. Did the period of loss of consciousness start suddenly or slowly?
6.28.2. Did it continue until death?
6.29. Did [*participant's name*] have convulsions?
6.29.1. For how long before death did the convulsions last?
6.29.1.1. Minutes:
6.29.1.2. Hours:
6.29.2. Did the person become unconscious immediately after the convulsions?
6.30. Was [*participant's name*] in any way paralyzed?
6.30.1. Which were the limbs or body parts paralyzed?
6.31. Was the participant a woman?
****SECTION 4: QUESTIONS FOR WOMEN****
Questions for women only
7.1. Did [*participant's name*] have any swelling or lump in the breast?
7.2. Did [*participant's name*] have any ulcers (pits) in the breast?
7.3. Had [*participant's name*]’s periods stopped naturally because of menopause?
7.4. Did [*participant's name*] have vaginal bleeding after cessation of menstruation? (post-menopausal)
7.5. Was she pregnant at the time of death or in the 6 weeks prior to her death?
7.5.1. For how many months was she pregnant?

7.6. Did she die during labour or delivery? (“Labour” is the period of time by which contractions are less than 10 minutes apart.)
Tobacco
8. Did [*participant's name*] use tobacco?
Healthcare and Health Records
9. Was care sought outside the home while the deceased had this illness?
Healthcare
9.1. Where or from whom did [*participant's name*] seek care? (CHECK ALL THAT APPLY)
9.2. Record the name and address of the government hospital where the care was sought:
9.3. Did a health care worker tell you the cause of death?
9.3.1. What did the health care worker say?

7.2.4 Appendix B4: Chichewa translation of the verbal autopsy questionnaire

Zodziwitsa
Malo
Namabala ya wogwira nchito ku dera
Namabala ya wotenga nawo mbali
Zokhudzana ndi wotenga nawo mbali
1.. Kodi wotenga nawo mbali tingalumikizane naye?
1.1. Chifukwa chani wotenga nawo mbali sitingalumikizane naye ?
1.2. Munthu womaliza munalankhula naye liti?
Chimene chinabweretsa imfa
2. Kodi pali chibale chotani pakati pa munthu amene akupereka uthenga ndi malemu?
3. Pali chikalata chotsimikiza za imfa cha kuchipatala ?
Chikalata chotsimikiza imfa cha ku chipatala.
3.1.Pali deti lanji pa chiphatso
3.2 kodi ICD code ilipo
ICD CODES
3.2.1.1. Lembani chimene chinabweretsa imfa kumapeto kuchokera pa chikalata cha kuchipatala
3.2.1.2.Lembani chinthu choyamba choganiziridwa chimene chinalebedwa kuti chinabweretsa imfa kuchokera pa chikalata cha kuchipatala
3.2.1.3. Lembani chinthu chachiwiri choganizirirdwa chimene chinalembedwa kuti chinabweretsa imfa kuchokera pa chikalata
3.2.1.4. Lembani chinthu choyamba chenicheni chimene chinabweretsa imfa kuchokera cha chikalata cha ku chipatala
3.2.1.5. Lembani chinthi chachiwiri
Zosalembedwa zobweretsa imfa
3.2.2.1 Lembani chimene chinabweretsa imfa kumapeto kuchokera pa chikalata cha kuchipatala
3.2.1.2.Lembani chinthu choyamba choganiziridwa chimene chinalebedwa kuti chinabweretsa imfa kuchokera pa chikalata cha kuchipatala
3.2.1.3. Lembani chinthu chachiwiri choganizirirdwa chimene chinalembedwa kuti chinabweretsa imfa kuchokera pa chikalata
3.2.1.4. Lembani chinthu choyamba chenicheni chimene chinabweretsa imfa kuchokera cha chikalata cha ku chipatala
3.2.1.5. Lembani chinthi chachiwiri
Kufufuza za imfa polankhulana
****Gawo 1: ZOVULALA NDI NGOZI**
4. Kodi [*dzina la wotenga nawo mbali*] anavulala kapena anachita ngozi imene inabweretsa imfa?
4.1. Kodi anavulala mwa mtundu wanji kapena anachita ngozi ya mtundu wanji [*dzina la wotenga nawo mbali*]?
4.1.1. Fotokozani zina :

4.2. Kodi kuvulalako anazipanga yekha kapena ngoziyo anayambitsa yekha?
4.3 Kodi kuvulala kunapangidwa ndi munthu wina kapena ngoziyo inapangidwa ndi munthu wina ?
****GAWO 2: MBIRI YA MATENDA A M'GONAGONA YA MALEMU****
5. Kodi [*dzina la wotenga nawo mbali nawo mbali**] anauzudwapo ndi a chipatala kuti iye amadwala chimodzi mwa zotsatirazi?
5.1 Mphumu
5.2 Kkhansa
5.3 Matenda a mgonagona a m'mapapo kapena mtima (COPD)
5.4 Matenda a shuga
5.5 Khunyu
5.6 Matenda a mtima
5.7Chifuwa chachikulu
5.8 Kufooka ziwalo
5.9 Edzi
**GAWO 3: M'NDANDANDA WA ZIZINDIKIRO
Mafunso amenewa akhudza m'mene munthu analili miyezi 12 asanamwalire [*dzina la wotenga nawo mbali*]
6.1 Kodi [*dzina la wotenga nawo mbali *] anatentha thupi ?
6.1.1 . Thupi linatentha kwambiri bwanj?
6.1.2Kodi kutentha thupi kumakhala bwanji?
6.2 Kodi [*wotenga nawo mbali*] anatuluka ziwengo?
6.2.1 Ziwengo zinali pati?
6.3 Kodi [*dzina la wotenga nawo mbali*] anali ndi zilonda?
6.3.1 Zilonda zianali ndi madzi kapena mafinya?
6.4. Kodi [*dzina ala wotemga nawo mbali*] anali ndi bala (lolowa) pa phanzi?
6.4.1 Bala limakha mafinya?
6.4.2 Bala linakha madzi mafinya angati?
6.5 Kodi [*dzina la wotenga nawo mbali*] amamva kubaya baya ngati "masingano" ku mapanzi awo?
6.6 Kodi [*dzina la wotenga nawo mbali*[anali ndi milomo ya blue.
6.7 [*dzina la wotenga nawo mbali*] anawonda m'miyezi itatu yomaliza asanamwalire?
6.7.1. Kodi anawonda muyezo wotani?
6.8 [*dzina la wotenga nawo mbali*] amaoneka kuti akusowa magazi?
6.9. [*dzina la wotenga nawo mbali*] anali ndi maso achikasu?
6.9.1 Kodi [*dzina la wotenga nawo mbali*] anakhala ndi maso a chikasu kwa nthawi yaitali bwanji?
6.9.1.1 Masiku:
6.9.1.2. Miyezi
6.10. [*dzina la wotenga nawo mbali *] amatupa mu kamfula?
6.10 [*dzina la wotenga nawo mbali*] watupa mu kamfula kwa nthawi yaitali bwanji?
6.10.1.1.Masiku
6.9.1.2 Miyezi
6.11. Kodi [*dzina la wotenga nawo mbali*]amatupa nkhope?
6.11.1 [*dzina la wotenga nawo mbali*] anatupa nkhope kwa nthawi yaitali bwanji?
6.11.1.1 Masiku

6.11.1.2 Miyezi
6.12 [*dzina la wotenga nawo mbali*] amatupa thupi lake lonse?
6.12.1 [*dzina la wotenga nawo mbali*] anatupa thupi lake lonse kwa nthawi yaitali bwanji ?
6.12.1.1 Masiku
6.12.1.2. Miyezi
6.13.1. Kodi [*dzina la wotenga nawo mbali*] anali ndi chotupa pakhosi?
6.13.2. Kodi [*dzina la wotenga nawo mbali*] anali ndi chotupa pa mkono?
6.13.3. kodi [*dzina la wotenga nawo mbali*] anali ndi chotupa pakati pa mwendo ndi mimba?
6.14. [*dzina la wotenga nawo mbali*] anali ndi chifuwa ?
6.14.1. [*dzina la wotenga nawo mbali*anadwla nthawi yaitali bwanji?
6.14.1.1. Masiku :
6.14.1.2. Miyezi
6.14.2. Kodi chifuwa chimatulutsa makhololo?
6.15 Kodi [*dzina la wotenga nawo mbali*] amakhosomola magazi
6.16 Kodi [*dzina la wotenga nawo mbali*]anali ndi mavuto popuma?
6.16.1 [*dzina la wotenga nawo mbali*] anali ndi mavuto pouma kwa nthawi yaitali bwanji?
6.16.1.1 Masiku :
6.16.1.2. Miyezi
6.16.2. Kodi kuvuka popuma kunali kongopitirira kapena mumabwera panthawi?
6.16.3. Kodi amavutika kwambiri akhala bwanji?
Kodi [dzina la wotenga nawo mbali*] amapuma mothamanga ?
6.17.1[*dzina la wotenga nawo mbali*] amapuma mothamanga kwa nthawi yaitali bwanji?
6.17.1.1.Masiku
6.17.1.2. Miyezi
6.18. Kodi [*dziana la wotenga nawo mbali*] amalira kukhosi popuma?
6.19 Kodi [*dzina la wotenga nawo mbali*] amamva kupweteka m'chifuwa mu mwezi umene anamwalira?
6.19.1 Kodi kupweteka kumeneku kunatenga nthawi yaitali bwanji?
6.19.2. Kodi kupweteka kumabwera pogwira ntchito ?
6.19.3. Kodi kupwetekaku kunali patipo?
6.20 Kodi [*dziana la wotenga nawo mbali*0 amachita chimbudzi cha madzi kawirikawiri kuposera masiku onse?
6.20.1 Kodi mu chimbudzi mumakhala magazi
6.20.2 Kodi mu chimbudzi mumakhala magazi mpaka nthawi yomwalira?
6.21 Kodi [*dzina la wotenga nawo mbali*] anasiya kukodza?
6.22 Kodi[dzina la wotenga nawo mbali*] amasanza mu sabata imene anamwalira
6.22.2 Kodi munali magazi mu masanzi?
6.22.2. Kodi masanzi anali akuda?
6.23 Kodi[*dzina la wotenga nawo mbali*] anali ndi mavuto pomeza?
6.23.1.[*dzian la wotenga nawo mbali*] anali ndi mavuto pomeza kwa nthawi yaitali bwanji asanamwalire ?
6.23.1.1 Masiku
6.23.1.2.
6.23.2. Kodi amavutika kumeza zolimba, zamadzi kapena zonse?
6.23.3 [*dzina la wotenga nawo mbali*] amava kupweteka pomeza?
6.24. [*dzina la wotenga nawo mbali*] amava kupweteka m'mimba?

6.24.1. [*dzina la wotenga nawo mbali*] anamva kupweteka m'mmba kwa nthawi yaitali bwanji?
6.24.1.1. maola
6.24.1.2. Masiku
6.24.1.3. miyezi
6.24.2 Kodi ululu unali m'mwamba kapena m'munsi mwa mimba?
6.25 [*dzina la wotenga nawo mbali*] anakula mimba kuposera mmene inalili?
6.25.1Kodi mimba inakhala yotupa kwa nthawi yaitali bwanji?
6.25.1.1 Masiku
6.25.1.2 Miyezi
6.25.2 . Kodi mimba ya [*dzina la wotenga nawo mbali *] imakula mwachangu bwanji?
6.26 Kodi m'mimba mwa [*dzina la wotenga nawo mbali*] munali madzi?
6.26.1. [*dzina la wotenga nawo mbali*] anakhala ndi madzi m'mimba kwa miyezi ingati ?
6.26.1.1 Masiku
6.26.1.2. Miyezi
6.27. Kodi [*dzina la wotenga nawo mbali*] amauma khosi?
6.27.1. Kodi [*dzina la wotenga nawo mbali anakhala ndi khosi louma kwa nthawi yaitali bwanji ?
6.27.1.1 Masiku [*Dzina l
6.27.1.2 Miyezi
6.28. Kodi [*dzina la wotenga nawo mbali*] ankhalapo chikomokere
6.28.1 Kodi nthawi imene anakhala chikomokere chinangochitika mwadzidzidzi kapena zinayamba pang'onopang'ono/
6.28.2. Kodi zinapiritiria mpaka anamwalira ?
6.29. Kodi [*dzina la wotenga nawo mbali*] amakomoka komoka ?
6.29.1 Kodi amakomokakomoka kwa nthawi yaitali bwanji asanamwalire?
6.29.1.1 Mpindi
6.29.1.2. Maola
6.29.2.Kodi muthuyo anakhala chikomokere zitangochitika zokomokakomoka?
6.30 Kodi [*dzina la wotenga nawo mbali*] anafooka ziwalo?
6.30.1. Kodi ndi ziwalo ziti kaoena mbali iti imene inafooka?
6.31. Kodi wotenga nawo mbali anali wamkazi kapena wammuna ?
**GAWO 4: MAFUNSO A AKAZI
Mafunso okhudza amai basi
7.1 Kodi [dzina la wotenga nawo mbali*] anali ndi zotupa kapena mbulu mu bere?
7.2 [*dzina la wotenga nawo mbali*] anali ndi mabala (olowa) m'mabere ?
7.3 Kodi [*dzina la wotenga nawo mbali*] anasiya kusamba chifukwa nthawi inakwana ?
7.4[*dzina la wotenga nawo mbali*] amasamba atasiya kale kusamba ?
7.5 .Kodi anali ndi mumba pamene amawalira kapena miyezi isanu ndi umodzi asanamwalire ?
7.6 Kodi anamwalira panthawi imene anali pa matenda kapena pobereka?
('pa matenda" ndi nthawi imene kupweteka kumakhala kotalikirana mpindi khumi)
FODYA
8.Kodi [*dzina la wotenga nawo mbali *] amasuta fodya?

Chisamalira cha ku chipatala ndi zolemba zokhudzana ndi umoyo
9. Kodi chisamaliro chimachokera kunja pamene malemu amadwala?
Chisamaliro cha kuchiapatala
9.1 [*dzina la wotenga nawo mbali*] Amapeza chisamaliro kuti? (ONANI ZIMENE ZIKUGWIRIZANA)
9.2 Lembani dzina ndi keyala ya chipatala cha boma kumene anakalandira chithandizo:
9.3 Kodi ogwira ntchito za umoyo anakuuzani chimene chinabweretsa imfa ?
9.3.1. Kodi wogwira ntchito za umoyo anati chani?

7.2.5 Appendix B5: Chichewa translation of the core questionnaire

NDONDOMEKO YA MAFUNSO A BOLD CORE

Demographics

1. Kodi wolowanawo mukafukufukuyi ndi mwamuna kapena mkazi? Mwamuna □

   mkazi □

2. Kodi ndinu mtundu wanji wa anthu? _____ ___ ___

3. Kodi munabadwa liti? ____ ____/____ ____/____ ____ ____ ____
   d d m m y y y y

4. Kodi sukulu munalekezera pati? (Zaka) ___ ___

5. Kodi maphunziro anu mwafika nawo pati Pulayimale sukulu □
   Pakali ano?
   Sekondale sukulu □
   Ma koleji ena □
   Sukulu ya ukachenjede/umisili □
   palibe □
   sizikudziwika □

6. Kodi abambo anu maphunzilo awo adalekezera pati? Pulayimale sukulu □

   Sekondale sukulu □
   Makoleji ena (Trade/Professional/Community) □
   Koleji ya ukachenjede/umisili □
   palibe □
   sizikudziwika □

6.1 Kodi amai anu maphunziro awo adelekezera pati? Pulayimale sukulu □

   Sekondale sukulu □
   Makoleji ena □
   Kolei yaukachenjede/yaumisili □
   palibe □
   sizikudziwika □

6.2. Chonde tandiuzeni ngati nyumbayi kapena wina aliyense nyumbamu ali/anagula zinthu izi

werengani chinthu chinachilichonse:	EYA	AYI	SIZIKUDZIWIKA
a. magetsi?	❑	❑	❑
b. chimbudzi chogejemula?.....	❑	❑	❑
c. lamya wa pansi	❑	❑	❑
d. lamya ya m'manja? .....□□□□□□□□□□□□	❑	❑	❑
e. kanema?	❑	❑	❑
f. wailesi?	❑	❑	❑
g. friji?	❑	❑	❑
h. galimoto?	❑	❑	❑
i. Thutumula ya moto?	❑	❑	❑
j. Makina wochapila zovala?	❑	❑	❑
k. nyumba yawo yogula okha.....	❑	❑	❑
l. bafa ya m'nyumba kapena shawa.....	❑	❑	❑
m. mpope wa madzi wa nyumba.....	❑	❑	❑
n. mpope wapanja wawo wawo.....	❑	❑	❑

q. Mu chaka chapitachi inuyo kapena wina aliyense wa nyumba mwanu, alipo amene anakhapo ndi njala chifukwa chosowa ndalama? □

□□masiku ambiri
□□milungu ya mbiri
□□miyezi ya mbiri
□□nthawi zina pa chaka
□□nthawi ndi nthawi
□ ndikale lonse.....

6.3 Pa nthawi yomwe munali ndi zaka zisanu alipo amene mumakhala naye nyumba mwanu limodzi anali ndi/anagula zinthu izi;

Werengani chinachilichonse	EYA	AYI	SIZIKUDZIWIKA
a. magetsi?	❑	❑	❑
b. chimbudzi chogejemula?	❑	❑	❑
c. l amya yapansi?	❑	❑	❑
d. kanema wa zinthunzi?	❑	❑	❑
e. wailesi?	❑	❑	❑
f. firiji?	❑	❑	❑
g. galimoto?	❑	❑	❑
h. Moped/scooter/njinga ya moto?	❑	❑	❑
i.makina wochapila zovala?	❑	❑	❑
j. kugula nyumba yawo yawo.....	❑	❑	❑
k. bafa ya m'nyumba kapena shawa.....	❑	❑	❑
l. mpope wa m'nyumba.....	❑	❑	❑
m. mpope wa panja wawowawo.....	❑	❑	❑

p. Kukhala ndi njala chifukwa chosowa ndalama? □

masiku ambiri
milungu ya mbiri
miyezi ya mbiri
nthawi zina pa chaka
mwa panthawi
ndi kale lonse.....

6.4. Kodi mukhala anthu angati m'nyumba mwanu(kuphatikizirapo inuyo) __ __

6.5. Kodi nyumba yanu ili ndi zipinda zingati? (osawelengera kitchini kapena bafa) __ __

Zizindikilo ndi matenda a kapumidwe

Mafunso awa ndi okhudzana mchifuwa chanu. Chonde yankhani kuti eya kapena ayi ngati kuli kotheka. Ngati mukaikila kuti yankho lanu ndi eya kapena ayi chonde lembani kuti ayi.

kukhosmola

7. Kodi nthawi zambiri mumakhosmola pamene mulibe chifuwa? Eya

Ayi

[ngati eya , pitilizani ndi funso nambala 7A; ngati ayi pitani ku funso nambala 8]

7A. Kodi pali <u>miyezi</u> imene mumakhosomola <u>masiku ambiri</u>? Eya

Ayi

[ngati ayankha eya, funsani mafunso <u>anse</u> awiri funso nambala 7B ndi 7C; ngati ayankha ayi pitaniku funso nambala 8]

7B. Kodi mumakhosomola <u>masiku ambiri</u> okwanila miyezi itatu pa chaka chinachilichonse? Eya

Ayi

7C. Kodi ndi kwa zaka zingati zimene mwakhala ndi chifuwa chimenechi? Kwa zaka zochepera ziwiri

pakati pa zaka ziwiri ndi zisau

pyolora zaka zisanu

<u>makhololo</u>

8. Kodi nthawi zambiri mumatulitsa <u>makhololo</u> anu kuchokera <u>mchifuwa,</u> kapena nthawi zambiri mumakhala ndi makhololo amene mumavutika kuwatulutsa Eya

ngati musakudwala chifuwa? Ayi □

[ngati ayankha eya pitilizani ndifunso nambala 8A; ngati ayankha ayi, pitani ku funso nambala 9]

8A. Kodi pali miyezi ina imene mumatulutsa makhololo masiku ambiri Eya □
Ayi □

[ngati eya funsani mafunso onse awiri, funso nambala 8B ndi 8C; ngati ayi pitani kufunso nambala 9]

8B. Kodi mumatulutsa makhololo amenewa kwa masiku ambiri mwina kwa miyezi itatu pa chaka? Eya □
Ayi □

8C. Kodi ndi kwa zaka zingati zomwe mwakhala ndi makhololo? Kosachepera zaka ziwiri □
pakati ma zaka ziwiri ndi zisanu □
kupyolera zaka zisanu □

Kusokosera mpweya m'chifuwa

9. kodi munanvapo kusokosera mpweya (wheezing or whistling) m'chifuwa mwanu nthawi ina iliyonse kwa miyezi khumi ndi iwiri yapitayi ? Eya □
Ayi □

[ngati ayankha eya, funsani mafunso onse nambala 9A ndi nambala 9B; ngati ayankha ayi, pitani ku funso nambala 10]

9A. Kwa miyezi khumi ndi iwiri yapitayi, munanvapo kusokosera mpweya (wheezing or whistling) m'chifuwa mwanu pokhapokha mutadwala chifuwa? Eya □
Ayi □

9B. Kwa miyezi khumi ndi iwiri yapitayi, munanvapo kusokosera mpweya (wheezing or whistling) m'chifuwa zimene zinakupangitsani kubanika? Eya □
Ayi □

Kubanika

10. Kodi mumalephera kuyenda chifukwa cha zinthu zina kapena matenda ena kupatula kubanika Eya□
Ayi□

[Ngati ayankha eya ku funso nambala 10, chonde longosolani bwinobwino za vutoli mzere uli munsiwu ndipo pitani pa funso nambala 12. Ngati yankho lili ayi kapena akukaikila, pitani pa funso nambala 11.]

vuto: _____

11. Kodi mumavutika ndi kubanika pamene mukuyenda mofulumira pa malo a fulati kapena
mukuyenda mtunda waung'ono? Eya ☐
Ayi ☐
[ngati ayankha eya, funsani funso nambala 11A mpakana 11D; ngati ayankha kuti ayi, pitani pa funso nambala 12]

11A. Kodi mumayenera kuyenda pang'onopang'ono kusiyana ndi anthu a msinkhu wanu pa malo opanda zitunda chifukwa Cho banika? Eya ☐
Ayi ☐
Sizikugwilizaana ☐

11B. Kodi mumapumira kaye mukamyenda pa mulingo wanu pa malo opanda zitunda? Eya ☐
Ayi ☐
Sizikugwilizaana ☐

11C. Kodi mumayenera kupumira mutayenda mtunda wokwanira 100 (kapena kwa mpindi zochepa) kwa malo opanda zitunda? Eya ☐
Ayi ☐
Sizikugwilizaana ☐

11D. Kodi mumabanika mukamatuluka nyumba kapena panthawi imene mukuvala kapena mukuvula chovala? Eya ☐
Ayi ☐
Sizikugwilizaana ☐

12. Kodi adokotala kapena ena a zaumoyo anayambapo atakuwuzanipo kuti muli ndi nthenda ya m'mapapo yomwe imapangitsa kuti mubanike? Eya ☐
Ayi ☐

13. Kodi adokotala kapena ena azaumoyo ankuwuzaniponi kuti muli ndi nthenda ya mphumu, chifuwa chokhudzana ndi mphumu, kapena

matenda ena aliwonse okhudzana ndi njira yopumira? Eya ☐

Ayi ☐

[ngati ayankha eya, funsani funso nambala 13A. Ngati ayankha ayi pitani ku funso nambala 14]

13A. Kodi mukanali ndi nthenda ya mphumu, chifuwa chokhudzana ndi mphumu,kapena matenda ena aliwonse okhudzana ndi njira yopumira?
Eya ☐
Ayi ☐

14. Kodi adokotala kapena a zaumoyo anyambapo akuwuzani kuti muli ndi matenda a chifuwa cha m'gona gona Eya ☐
Ayi ☐

[ngati ayankha kuti eya, funsani funso nambala 14A. Ngati aynkha kuti ayi, pitani ku funso nambala 15]

14A. Kodi mukadali nayo nthenda ya chifuwa cha m'gona gona Eya ☐

Ayi ☐

15. Kodi adokotala kapena a zaumoyo anayamba akuwuzaniponi kuti muli ndi nthenda yam'gonagona yokhudzana ndi kutsekeka kwa njira yopumira? Eya ☐
(COPD) Ayi ☐

Management Section

Pano ndikufunsani zokhudzana mankwala amene mukhonza kumwa kuti akuthandizeni ku mapumidwe. Ndikufuna kuti ndidziwe za mankhwala amene mumamwa kawirikawiri komanso mankhwala amene mukhonza kumwa kuti mungochepetsa ululu wa vutolo. Ndikufuna mundiwuze mankhwala ena aliwonse amene mumamwa, njira yake komanso mumagwritsa ntchito mowirikiza bwanji pa mwezi wina uliwonse.

16. Mu miyezi khumi ndi iwiri yapitayi, kodi mwamwapo mankhwala a vuto la mapumidwe kupahatikizapo mankhwala Oletsa kuti phuno zisatseke? Eya ☐

Ayi ☐

Ngati otenga nawo mbali sakumwa mankhwala ena aliwonse owathandiza mbali ya mapumidwe awo, pitani ku funso nambala 17.

16A. Dzina la Mankhwala (sinalewmbedwe)							
16B. Nambala ya mankhwala	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___
16C.Kapangidwe	mb'ulu wa ❑ mankhwala ❑ Inhaler ❑ Nebulizer ❑ A madzi ❑ Suppositori ❑ Jakisoni Ena	mb'ulu ❑ wmankhwa ❑ Inhaler ❑ Nebulizer ❑ A madzi ❑ Suppositori ❑ Jakisoni Ena	mb'ulu wa ❑ mankhwala ❑ Inhaler ❑ Nebulizer ❑ A madzi ❑ Suppositori ❑ Jakisoni Ena	mb'ulu wa ❑ mankhwala ❑ Inhaler ❑ Nebulizer ❑ A madzi ❑ Suppositori ❑ Jakisoni Ena	mb'ulu wa ❑ makhwala ❑ Inhaler ❑ Nebulizer ❑ Amadzi ❑ Suppositori ❑ Jakisoni Ena	mb'ulu wa ❑ mankhawa ❑ Inhaler ❑ Nebulizer ❑ Amadzi ❑ Suppositori ❑ Jakisoni Ena	mb'ulu wa ❑ mankhwala ❑ Inhaler ❑ Nebulizer ❑ Amadzi ❑ Suppositori ❑ Jakisoni Ena
16D. Kodi mankhwala wo amamwedwa masiku onse kapena nthawiyomwe muli ndi zizindikilo, kapena zonse (*ngati ayankha kuti 'masiku onse' afunseni fnso nambala 16 16 F , ngati*	Masiku ons ❑ zizindikilo ❑ zonse ❑ zina	Masiku on ❑ zizindikilo ❑ zonse ❑ zina	Masiku or ❑ zizindikilo ❑ zonse ❑ zina	Masiku or ❑ zizindikilo ❑ zonse ❑ zina	Masiku or ❑ zizindikilo ❑ zonse ❑ zina	Masiku or ❑ zizindikilo ❑ zonse ❑ zina	Masiku or ❑ zizindikilo ❑ zonse ❑ zina

ayankha kuti 'zonse' funsani mafunso onse funso nambala 16E ndi 16 F)							
16E. Nthawi yomwe mukumwa mankhwala, kodi mumamwa masiku angati pa mulungu?	__masiku/mulungu	__masiku/mulungu	__masiku/mulungu	__masiku/mulungu	__masiku/mulungu	__masiku/mulungu	__masiku/mulungu
16F. Nthawi yomwe munamwa mankhwalawo, kodi ndi miyezi ingati pa miyezi khumi yapitayi imene mwamwa mankhwalawo?	0-3 □ 4-6 □ 7-9 □ 10-12 □	0-3 □ 4-6 □ 7-9 □ 10-12 □	0-3 □ 4-6 □ 7-9 □ 10-12 □	0-3 □ 4-6 □ 7-9 □ 10-12 □	0-3 □ 4-6 □ 7-9 □ 10-12 □	0-3 □ 4-6 □ 7-9 □ 10-12 □	0-3 □ 4-6 □ 7-9 □ 10-12 □

17. chonde tandiwuzeni zinthu zomwe mumamwa kapena zomwe mumachita kuti zikuthandizeni kumbaliya vuto lamapumidwe zimene simunandiwuze

Mankhwala kapena zochita	nambala
	____ ____ ____
	____ ____ ____
	____ ____ ____
	____ ____ ____

18. Kodi adokotala kapena azaumoyo anakuyezaniponi mapapo ndi makina oyezera mpweya? (mwachitsanzo spirometer or peakflow meter) Eya ☐

Ayi ☐

[ngati ayankha kuti eya,funsani funso nambala 19A Ngati ayankha kuti ayi, pitani ku funso nambala 19]

18A. Kodi mwagwiritsapo ntchito makina amenewa pa miyezi khumi ndi iwiri yapitayi? Eya ☐

Ayi ☐

19. Kodi munali ndi nthawi imene munavutika kupuma kwambiri mpakana kuti kunali kovuta kuti mugwire ntchito zanu za tsiku ndi tsiku kapena kulephera kupita ku ntchito? Eya ☐

Ayi ☐

[ngati yankho lili eya, funsani funso nambala 19A Ngati anena kuti ayi, pitani kufunso nambala 20]

19A. Kodi vuto ngati limeneli munakhala nalo kangati miyezi khumi ndi iwiri yapitayi? ____ ____ ____ vutolo

[ngati anali ndi vuto limeneli, funsani funso nambala 19B ndi 19C ngati ayi pitani ku funso nambala 20]

19B. Pa mavuto amenewa ndi kangati munawonana ndi adotolo kapena ogwira ntchito m'chipatala kwa miyezi Khumi ndi iwiri yapitayi? _____ _____ vutoli

19C. Pa mavuto amenewa kodi munayamba mwago nekedwapo m'chipatala miyezi khumi ndi iwiri yapitayi?

_____ _____ vutoli

[ngati 19C >0, funsani funso nambala 19C1, else pitani ku funso nambala 20]

19C1. Kodi ndi masiku angati amene munagonekedwa m'chipatala chifukwa cha vuto la mapumidwe mu miyezi khumi ndi iwiri yapitayi ____ ____ ____ masiku

kusuta fodya

20. Tsopano ndikufansani zosuta fodya. Poyambilira ndikufunsani za ndudu, kuphatikiza wopichila nokha, kenaka ndizakufunsani za fodya wina amene amasutidwa.

20.1. Kodi munayambapo mwasutapo fodya? Eya ☐
Ayi ☐

("eya" amatanthauza ma paketi a ndudu opyolera makumi awiri mu moyo wawo kapena ndudu yopyolera imodzi pa tsiku kwa chaka)

[ngati ayankha kuti eya, funsani funso nambala 20A mpakana 20D ngati ayi pitani ku funso 20.2]

Kodi munali ndi zaka zingati nthawi imene mumayamba kusuta
_____ ____

Ngati munasiya kusuta, kodi mwasiya kusuta muli ndi zaka zingati?
ngati wotenga nawo mbali kusutabe lembani kuti '999' _____ _____

C. Kodi mumasuta fodya mungati patsiku kapena Pamulungu.? i)____ ____ ____ ndudu pa tsiku
ii)___ ____ ____ ndudu pamulungu

Kodi mumasuta fodya wopangidwa ku kampani kapena fodya wopichira nokha, Wopangidwa ku kampani ☐

wopichira ☐

20.4. Kodi munayambapo mwasuta fodya wamu kaliwo? Eya ☐
Ayi ☐

("eya", akutanthauza kuti ansutapo ma ounce opyolera khumi ndi awiri a pipe tobacco mu moyo wawo)

[ngati ayankha kuti eya, funsani mafunso kuyambila funso namala 20.4A mpakana 20.4C ; ngati ati ayi pitani ku funso nambala 20.5]

Kodi munali ndi zaka zingati pamene munayamba kusuta pafupi pafupi fodya wa mu Kaliwo _____ _____

Ngati munasiya kusuta, kodi munasiya muli ndi zaka zingati? (ngati wotenga nawo mbali sanasiye kusuta lembaniponi kuti '999') _____ _____

Kwa nthawi yonse imene mwakhala mukusuta kapena imene munkasuta, kodi mumasuta mapipe angati patsiku kapena pa mulungu? (wonani pa ndondomeko wa mafunso A MRC) i)____ ____ ____ grams/pa tsiku
ii)____ ____ ____grams/pa mulungu

20.5. Kodi munayambapo mwasuta cigars, cheroots, or cigarillos? Eya ☐
Ayi ☐

("Eya", akutanthauza kuti ndudu yopyolera imodzi ya cigar /ya cheroots / ya cigarillos pa mulungu kwa chaka mu muyo wawo)

[ngati ayankha kuti eya, funsani mafunso nambala 20.5A mapakana 20.5 C; ngati ati ayi, pitani ku funso nambala 20.6]]

A. Kodi munayamba kusuta fodya wa cigar/cheroot/cigarillos muli ndi zaka zingati? _____ _____

B. Ngati munasiya kusuta fodya, kodi munali ndi zaka zingati m'mene munkasiya? (ngatiwotenga nawo mbali sadasiye, lembaniponi kuti '999') _____ ____

C. Kwa nthawiyonse imene mwakhala mukusuta kapena imene munkasuta kodi mwasutapo

ndudu zingati pa tsiku kapena pa mulunngu? i) __ ___ ___ cigars etc/pa tsiku
ii)__ __ __cigars etc/pa mulungu

Note: Mutha kufinsa mafiso: 20.7 ndi 20.8 kapena ayi

20.7. munayambapo mwasutapo fodya wa chamba? Eya
☐
Ayi ☐

("eya," akutantawuaza kusuta majoints wo pyolela makumi awiri m'moyo wawo kapena joint imodzi pa mwezi kwa chaka nthawi inam iliyonse m'moyo wawo)

[ngati ayankha kuti eya funsani mafunso kuyambila funso nambala 20.8A mpakana 20.8C; ngati ati ayi pitani ku funso nmabala20.8)

Kodi munali ndi zaka zingati pamene munayamba
kusuta pafupipafupi fodya wa chamba? _____ _____

Ngati munasiya kusuta, kodi munasiya kusuta muli
ndi zaka zingati? (ngtiwotenganawo mbali sanasiye
lembaniponikuti '999') _____ _____

Nthawiyonse imene mwakhala mukusuta kapena
imene munkasuta, kodi mumasuta ndudu zingati
za chamba patsiku kapena pa mulungu? i)___ ____ ___ joints/pa tsiku
ii)___ ___ ___ joints/pa mulungu

20.8.Kodi munayambapo mwasutapo kapena kupumira mkati zinthu
Zokhala ngati fodya? Eya ☐
Ayi ☐
20.8.1. Mtundu _____
20.8.2. Mulingo/Kuchuluka _____

[ngatiayankha kuti eya, funsani mafunso kuyambila funso nambala 20.8A mpakana 20.8C; ngati ati ayi, pitani kufunso nambala 21)

A.Kodi munali ndi zaka zingati pamene munayamba __ __
(_____) kusuta?

B. Ngati mudasiya kusuta, kodi mudasiya muli ndi zaka zingati? (ngati

wotenga nawo mbalisadasiye lembaniponi kuti ‘999’) _____ _____

Kwa nthawi imene mwakhala mukusuta kapena imene munkasuta mumasuta fodya ochuluka bwanji angati pa tsiku kapena pa mulungu? i)__ __ __ unit/pa tsiku

ii)__ __ __unit/pa mulungu

[ngatiwotenga nawo mbali akusutabe fodya (funso nambala 20B palembedwa kuti ‘999,) ndiyeno funsani funso nambala 21A ndi 21B, ngati ati ayi pitani ku funso nambala 23]

21A. Mu chaka chapitachi, kodi mwasiyapo kusuta kangati kwa tsiku limodzi ____ ____ ____

21B. Kodi muli ndi malingaliro osiya kusuta pakadali pano? Eya, mkatikati mwa masiku makumi atatu akudzawa. ☐ Eya, mkatikati mwa miyezi isanu ndi umodzi ikudzayi. ☐

Ayi, sindikuganizirako zosiya kusuta. ☐

[ngati wotenganawo mbali sanasutepo fodya (wayankha kuti ayi ku ma funso ans kuyambila nambala 20.1 mapkana 20.5), ndiyepitaniku funso nambala 24.1. ngati ati eya pitilizani ndifunso nambala 23] pakadali pano palibepo funso nambala 22.

23. Kodi adotolo kapena a zaumoyo adakulangizaniponi kuti musiye kusuta fodya? Eya ☐

Ayi ☐

[ngati ayankha kuti eya, fusani funso nambala 23Andi 23B, ngati ati ayi, pitani ku funso nambala 24]

23A. Kodi mwalangizidwapo kuti musiye kusuta fodya mu miyezi khumi ndi iwiri yapitayi? Eya ☐

Ayi ☐

23B. Kodi mwagwiritsapo ntchito mankhwala ena aliwonse (Motsogoleledwa ndi adokotala kapena ayi) kuphatikizapo Makhwala omata pakhungu a nikotini kuti musiye kusuta? Eya ☐

Ayi ☐

[ngati ayankha kutimeya, funsani funso nambala 23B1, kenako funsani funso nambala 24. Ngati ati ayi pitani ku funo nambala 24]

23B1.Kodi ndi mtundu wanji wa mnkhwala umene

Munamwa kuti ukuthandizeni kusiya kusuta
Fodya? Nicotine Replacement ☐
Buproprion ☐
Tofranil ☐

Mankhwala ena ☐

24. Kodi mwagwiritsapo kapena kuchita china chilichonse
Kuti musiye kusuta fodya? Eya ☐
Ayi ☐

[ngati ayankha kuti eya, funsani funso nambala 24A, ngati ati ayi, pitani ku funso nambala 24.1]

24A. Kodi munapanga chani? Hypnosis ☐
Acupuncture ☐
Biofeedback ☐
Njira ina ☐

24.1. Osaziwerengelapo inuyo, kodi ndi anthu angati m'nyumba mwanu amene amasuta fodya pafupipafupi. __ __

24.2. Kodi anthu amsuta pafupipafupi fodya mu chipinda ku malo anu ogwirako ntchito? Yes ☐ No ☐
sagwira ntchito ☐

24.3. Kodi ndi ma ola angati patsiku amene mumayandikilana ndi anthu ena osuta fodya ku malo ngati awa?

24.3.1. ku nyumba ___ __

24.3.2. ku malo agwra ntchito ___ __
24.3.3. ku malo omwera mowa, odyera zakudya
Owonwera kanema wa zinthunzi, kapena malo
osangalalako akapangidwe koterowo ___ __
24.3.4. malo ena aliwonse ___ __

24.4. Kodi abambo anu anayambapo asuta fodya pafupipafupi nthawi yomwe munali mwana?
Eya ☐
Ayi ☐

24.5. kodi amayi anu anayambopo asuta fodya nthawi ya utsikana wawo ? Eya ☐ Ayi ☐

Chidziwitso, kakhalidwe ndinjira zomwe tingazindikile msanga za kusintha mukuwona ndikunva

Chiyambi: mafunso otsatirawa ndi okhudzana ndi ndudu ndi fodya

24.6. Kutengera pa zomwe mukudziwa kapena zomwe mumakhulupilira,Kodi kusuta fodya kukapangitse munthu kudwala kwambiri Eya ☐☐ Ayi ☐

[ngati ayankhakuti eya, funsani funso nambala 24.7, ngati ati ayi pitani ku funso nambala 25]

24.7. Kutengera pa zomwe mukudziwa kapena mumakhulupilira kodi kusuta fodya kungapangitse……

Werengani chinthu chinachilichonse	EYA	AYI	SINDIKUDZIWA
nthenda yo kufa ziwalo(magazi oundan na a muobongo amene amapangitsa kufa kwa ziwalo?	❑	❑	❑
b. Nthenda ya mtima?.....	❑	❑	❑
c. Khasa ya mapapo?.....	❑	❑	❑
d. Chifuwa cha mg'onagona?.....	❑	❑	❑
e. Matenda mg'onagonokhuzana ndi mapapo.	❑	❑	❑
ntchito	❑	❑	❑

25. Kodi munagwirapo ntchito malo afumbi kwa chaka kapena kupyolera? Eya ☐

Ayi ☐

[ngati ayankha kuti eya, funsani funso nambala 25A nagti ati ayi, itani ku funso nambala 26]

25A. Mwakhala kwa zaka zingati mukugwira malo a fumbi? _____ _____

Zinthu zina zingaonjezere kusapeza bwino

26. Kodi adotolo kapena ena aliwonse a za umoyo adakuwuzanipo kuti muli ndi nthenda ya :

26A. Mtima Eya ☐

Ayi ☐

26A. Kulephera kugwira ntchito kwa mtima

Eya ☐

Ayi ☐

26B. Vuto lothamanga magazi Eya ☐
Ayi ☐

26C. Matenda a shuga Eya ☐
Ayi ☐

26D. Khansa ya mapapo Eya ☐
Ayi ☐

26E. Kufa ziwalo Eya ☐
Ayi ☐

26F. Chifuwa chachikulu Eya ☐
Ayi ☐

[ngati ayankha kuti eya, ku funso nambala 26F ndiye funsani funso nambala 26F1; ngati ati ayi, pitani ku funso nambala 27]]

26F1. Kodi mukumwa mankhwala a chifuwa cha chikulu? Eya ☐
Ayi ☐
[ngati ayankha kuti ayi ku funso nambala 26F1 , ndiye funsani funso nambala 26F2; ngati akuti eya pitani ku funso nambala 27]

26F2. Kodi munayambapo mamwa mankhwala a chifuwa chachkulu? Eya ☐

Ayi ☐

27. Kodi munayambapo mwa pangidwa opareshoni pa chifuwa imene inachititsa kuchotsapo mbali imodzi la phapo lanu?Eya ☐
Ayi ☐

28. Kodi munayambapo mutagonekedwa m'nchipatala ndi vuto lokanika kupuma musanakwanitse zaka khumi? Eya ☐
Ayi ☐
sindikudziwa ☐

29. Mu miyezi khumi ndi iwiri yapitayi, munalandilapo katemera wa chimfine? Eya ☐
Ayi ☐
sindikudziwa ☐

30. Kodi adotolo kapena azaumoyo adawauzapo bambo anu, mayi anu, chemwali wanu kapena nchimwene wanu kuti ali

ndi nthenda ya m'mapapo yomwe imapangitsa kubanika, chifuwa cha m'gona gona kapena matenda otseka njira yo pumira (COPD)? Eya ☐
Ayi ☐

31. kodi pali anthu ena a nyumba mwanu (kupatulapo inuyo) asutapo fodya wandudu kaliwo kapena chi ndudu chachikulu musabata ziwiri zapitazi? Eya ☐
Ayi ☐

SF12

Ofunsa mafunso: werengani malangizo kwa munthu ofunsidwa.
Malangizo: kafukufukuyu ndi ofuna kudziwa mmene thanzi lanu lilili. Izi zithandiza ku londoloza za mmene inuyo mumanvera nthupi mwanu ndiponso mmene mumagwirila ntchito zanu za tsiku ndi tsiku. Pa funso linalilonse chonde sankhani funso lomwe mukuliwona kuti likukamba bwino za inuyo.

32. Munganenepo chani za umoyo wanu : *(Check one)* labwino kwa mbiri zedi ☐

La bwino kwa mbiri ☐
Labwino ☐
lilibwinoko ☐
sililibwino ☐

33. Mafunso ali munsimu ndi okhudzana ndi zomwe mungachite tsiku ndi tsiku. Kodi nthanzi lanu panopa limakulepheretsani kugwira ntchitozi? Ngati zili choncho, zimakulepheretsani bwanji?

33A. *Ntchito zopepukirapo*, ngati kusuntha gome Kukolopa kusewera masewero a mpira kapena kusewera Ntchito za kudimba. eya, ndimakanika kwambiri ☐

Eya, ndimakanika pang'ono ☐
sindimakanika ☐

33B. Kukwera ma sitepe angapo? Eya,Ndimakanika kwambiri ☐

Eya Ndimakanika pang'ono ☐

Sindimakanika ☐

34. Kodi mu milungu inayi yapitayi, kodi ndikangati komwe mwakhala Ndi mavuto awa ndi ntchito yanu kapena mu ntchito zanu zina chifukwa cha umoyo wanu?

34A. Mumakwaniritsa mochepa kuyelekeza ndi monga Mmene mumayembekezera nthawi zonse ☐
Nthawi zambiri ☐
Nthawi zina ☐
Nthawi pango'ono ☐
palibe ☐

34B. Mumagwira ntchito kapena kupanga zinthu zina osati momwe mumapangira nthawi zonse nthawi zonse ☐
Nthawi zambiri ☐
Nthawi zina ☐
Nthawi pango'ono ☐
palibe ☐

35. Kwa milungu inayi yathayi, kodi ndi kochuluka bwanji komwe mwakhala ndi chimodzi chan mavuto ndi ntchito yanu kapena ntchito zanu za tsiku ndi tsiku kaamba ka vuto la maganizo?(monga ngati kukhumudwa)?

35A. Mumakwaniritsa mochepa kuyelekeza ndi monga Mmene mumayembekezera
nthawi zonse ☐
Nthawi zambiri ☐
Nthawi zina ☐
Nthawi pango'ono ☐
palibe ☐

35B.Mumagwira ntchito kapena kupanga zinthu zina osati momwe mumapangira nthawi zonse?
nthawi zonse ☐
Nthawi zambiri ☐
Nthawi zina ☐
Nthawi pango'ono ☐
palibe ☐

36. Kwa milungu inayi yapitayi, kodi ndikangati komwe ululu wanu wakulepheretsai kugwira ntchito zanu za tsiku ndi tsiku

palibe nkomwe ☐
pang'ono ☐
Mochulikirapo ☐
Mochuluka kwambiri ☐
Mochuluka kwambiri zedi ☐

37. Mafunsowa ndi okhudzana ndi m'mene mukunvera mthupi mwanu ndim'mene zinalili ndi inuyo pa milungu inayi yathayi. Pa funso linalilonse, chonde perekani yankho limodzi lomwe likulongosola moyenerera m'mene mwakhala mukunvera.

Kodi ndikangati pa milungu inayi yomwe ya pitayi….

37A.Momwe nthupi mwanu munamva bwino?

nthawi zonse ☐
Nthawi zambiri ☐
Nthawi zina ☐
Nthawi pango'ono ☐
palibe ☐

37B. Mumakhla ndi mphanvu zambiri? nthawi zonse ☐

Nthawi zambiri ☐
Nthawi zina ☐
Nthawi pango'ono ☐
palibe ☐

37C. Munakhala okhumudwa? nthawi zonse ☐

Nthawi zambiri ☐
Nthawi zina ☐
Nthawi pango'ono ☐
palibe ☐

38. Pa milungu inayi yapitayi, kodi kochuluka bwanji komwe Moyo wanuwo kapena vuto la maganizo anu lakulepheretsani kugwira ntchito kapena kuchita zochita zanu za tsiku ndi tsiku? (monga kuyendera anzanu, abale anu, ndi zina zotero)

nthawi zonse ☐
Nthawi zambiri ☐
Nthawi zina ☐
Nthawi pang'ono ☐
palibe ☐

Zokhudzana ndi zachuma

Nthawi ya ntchito yomwe inatayika

Mafunso otsatirawa ndi okhudzana ndi ntchito imene mumagwira komanso masiku amene mwajomba chifukwa cha vuto la umoyo wanu

39. Mwa miyezi khumi ndi iwiri yapitayi mwagwirapo ntchito yolipidwa? Eya ☐

Ayi ☐

[ngati ayi, pitilizani ndi funso nambla 39A; ngati eya, pitani kufunso nambala 44]

39A. Mwa miyezi khumi ndi iwiri yathayi, mwakanika kugwira ntchito yolipidwa Chifukwa cha vuto la mapumidwe? Eya ☐
Ayi ☐

39B. Mwa miyezi khunmi ndi iwiri yapitayi,simunagwire ntchito yolipidwa chifukwa munali wokhala pakhomo kapena mumasamalira wina? Eya ☐

Ayi ☐

[ngati eya, pitilizani ndi funso nambala 39C, ngati ayi, pitani ku funso nambala 40]

39C. Mwa miyezi khumi ndi iwiri yapitayi, kodi vuto la umoyo wanu linakulepheretsani ntchito zanu za pakhomo za masiku onse kapena kusamalira munthu wina wake? Eya ☐
Ayi ☐

[ngati eya, pitilizani ndi funso nambala 39D ndi funso nambala 39E, ngati ayi, pitani ku funso nambala44]

39D. Mu miyezi khumi ndi iwiri yathayi kodi ndi masiku angati omwe Mwalephera kupanga ntchito zanu zapakhomo kapena Kusamalira wina kaamba ka vuto la umoyo wanu? ____ ____ ____

39E. Mu miyezi khumi ndi iwiri yapitayi, kodi ndi masiku angati omwe mwalephera kugwira kapena kuchito ntchito zanu za pakhomo kapena kusamalira wina kaamba kweni kweni ka vuto la mapumidwe____ ____ ____

[chonde pitani ku funso nambala 44]

40. Kodi mwagwira ntchito yolipidwa kwa miyezi ingati mu miyezi khumi ndi iwiri yathayi? _____ _____

41. Munthawi imene mumagwirayi ntchito yolipidwayi, kodi ndi masiku angati pa Mulungu amene mumagwira ntchito? ____ _____

42.Kodi mumagwira ntchito yolipidwayi kwa maola angati pa tsiku? _____ _____

43.Mu miyezi khumi ndi iwiri yathayi, kodi vuto la umuyo wanu linakulepheretsani kugwira ntchito yolipidwayi? Eya ☐
Ayi ☐

[ngti eya, pitilizani ndi funso nambala 43A ndi 43B, ngati ayi, pitani ku fiunso nambala 44]

43A. Mu miyezi khumi ndi iwiri yathayi, kodi ndi masiku okwana angati Munalephera kugwira ntchito yolipidwa kaamba ka vuto la umoyo wanu? ____ ____ ____ days

43B. Mumiyezi khumi ndi iwiri yathayi, kwa masiku angati Amene munalephera kugwira ntchito yolipidwa kwenikweni kaamba ka vuto la mapumidwe? ____ ____ ____ days

zinthu zina zosakhudzana ndi ntchito zomwesizinakwanilitsidwe

Mafunso otsatirawa ndi okhudzana ndi nthawi yomwe yataidwa posakwanitsa ntchito zanu za tsiku ndi tsiku (monga kukagula zinthu, kuyendela anzanu/abale, kupita ku tchalichi kapena zinthu zina) chifukwa cha mavuto a umoyo wanu

44. Mu miyezi khumi ndi iwiri yathayi, kodi mavuto a umoyo wanu anakulepheretsani kutenga nawo mbali pa zochitika kamodzi kapena kawiri kawiri? Eya ☐
Ayi ☐

[ngati eya, yankhani funso nambala 44A ndi 44B, ngati ayi, pitani ku mawu olemba kuti yamalizidwa ndi kumapeto kwa ndondomeko ya mafunsowa]

44A. Mu miyezi khumi ndi iwiri yapitayi, ndi kwa masiku angati amene simunatengepo mbali mu zinthu zochitika zosagwirizana ndi ntchito zanu kaaba ka vuto la umoyo wanu? ____ ____ ____ days

44B. Mumiyezi khumi ndi iwiri yapitayi, kwa masiku angati amene simunatenge nawo mbali pa zinthu zochitika kaamba kwenikweni ka vuto la mapumidwe? ____ ____ ____ days

yamalizidwa ndi: ____ ____ ____ ____

7.2.6 Appendix B6: Chichewa translation of the spirometry questionnaire

TSAMBA LA NDONDOMEKO YA NTCHITO YOPHWEKA YOPEZA NDI KUYANG'ANILA MAVUTO A MAPAPO POGWIRITSA NTCHITO KUPUMA MU KAFUKUFUKU WA BOLD

Mafunso ofuna kukutetezani

1. Mu miyezi itatu yadutsayi mwapangidwapo opaleshoni ina iriyonse pachifuwa kapena pa mimba panu? Inde ☐ Ayi ☐

2. Kodi mwakhalapo ndi vuto la mtima mkati-kati mwa miyezi itatu yadutsayi? Inde ☐ Ayi ☐

3. Kodi muli ndi kachikopa kofewa kwambiri ka diso kapadela Kapena mwakhalapo ndi opaleshoni ya diso mkati-kati mwa miyezi Itatu yapitayi? Inde ☐ Ayi ☐

4. Kodi mwagonekedwapo mchipatala chifukwa cha vuto lina lirilonse la mtima mkati-kati mwa mwezi wapitawu? Inde ☐ Ayi ☐

5. Kodi muli gawo lachitatu la kukhala ndi pakati/ kwasala miyezi itatu kuti mu beleke? Inde ☐ Ayi ☐

6. Kodi otenga nawo mbariwa mtima wawo ukugunda kokwana mlingo 120 atangokhala akamapumula pa mphindi iriyonse? Inde ☐ Ayi ☐

7. Kodi pakali pano mukumwa mankhwala a TB? Inde ☐ Ayi ☐

8. *Kodi pali chifukwa china chimene otenga nawo mbari uyu Sakuyenera kupanga nawo ndondomeko ya ntchito yophweka yopeza ndi kuyang'anila mavuto a mapapo pogwiritsa ntchito kupuma?* Inde ☐ Ayi ☐

*ngati yankho ku ena aliwonse mwa mafunso 1 kudutsa 8 liri "Inde", **MUSA** pitilize ndi ntchito yoyezayi mapapo. Pitani ku gawo la zotsatira pomwe pali ntchito yophweka yopeza ndi kuyang'anila mavuto a mapapo pogwiritsa ntchito kupuma ndipo ikani chizindikiro pa mafunso 11A ndi 11B choti "Ayi", ndipo onani bokosi yachiwiri "otenga nawo mbari wachotsedwa pa nkhani ya mndandanda wa mankhwala", ku funso 11C.*

9. Kodi mwakhalapo ndi matenda okhudzana ndi kupuma (chinfine) mu masabata atatu adutsawa? Inde ☐ Ayi ☐

10.1. Kodi mwamwapo mankhwala ena aliwonse pa vuto la mapumidwe mu maola 24 apitawa? Inde ☐

Ayi □

*Ngati ali **Inde**, lembani dzina/mtundu wa mankhwala agwiritsidwa ntchito.*

_____

_____

_____

Ngati funso 10.1 liri Inde ndipo mankhwala agwiritsidwa ntchito akuphatikizapo ina iriyonse mwa mitundu yotsatira m'munsimu, pitani ku funso 10.2.ngati ali Ayi,pitani ku funso 10.5.

MTUNDU WA MANKHWALA	**ZITSANZO**	
Short-acting beta-2 agonist	albuterol, salbutamol	Maola 6 ife tisanafike panyumba pano
Anticholinergic inhaler	Atrovent, ipratropium	Maola 6 ife tisanafike panyumba pano
Long-acting beta-2 agonist (kuphatikizapo zosakaniza zokonzedwa zimene ziri ndi LABA)	Serevent, Advair, formoterol, Symbicort	Maola 12 ife tisanafike panyumba pano
Oral beta-2 agonist	Albuterol	Maola 12 ife tisanafike panyumba pano
Oral theophylline	Theodur	Maola 12-24 ife tisanafike panyumba pano.
Long-acting anticholinergic	Spiriva, tiotropium	Maola 24 ife tisanafike panyumba pano

10.2. *kodi otenga nawo mbari anagwiritsa ntchito **short-acting beta-2 agonist** kapena **anticholinergic inhaler,** kaya paokha kapena pophatikiza zinthu zina,mu maola asanu ndi chimodzi apitawa?* Inde □

Ayi□

10.3 *kodi otenga nawo mbari anagwiritsapo ntchito long-acting beta-2 agonist kapena ndi zinthu zina,mu maola 12 adutsawa?* Inde□

Ayi□

10.4. *kodi otenga nawo mbari anagwiritsilapo ntchito **Oral theophylline** /* **long acting anticholinergic,** *Kaya payokha kapena kuphatikiza zinthu zina/mankhwal, M'maola 24 apitawa?* Inde □

□□□□□□□□□□□□□□□□□□□□□□□□□□□Ayi □

10.5.Kodi mwasuta komaliza liti? i) maola____ ____ ____apitawa
ii) masiku____ ____apitawa

lembani 999 ngati ali osasuta kapena osiya kusuta (sanasutepo mu mwezi umodzi wapitawo)

10.7. Kugunda **bpm ___ ____ ____**

10.8. Kutalika **____ ____ ____cm**

10.9 Kulemela **____ ____ ____.____kg**

10.10.A. Muyezo oyamba wa mu malekezelo a ntchafu: **____ ____ ____.____cm**

10.10.B. Muyezo wachiwiri wa mu malekezelo a ntchafu **____ ____ ____.____cm**

10.11.A. Muyezo oyamba wa mu malekezelo a chiuno **____ ____ ____.____cm**

10.11.B. Muyezo wachiwiri wa mu malekezelo a chiuno **____ ____ ____.____cm**

Spirometry Outcome

11A.	Acceptable pre-bronchodilator test completed?	Yes ☐ No ☐
11B.	Acceptable post-bronchodilator test completed?	Yes ☐ No ☐
11C.	Unable to obtain satisfactory spirometry (check one)	
	The participant did not understand instructions	☐
	The participant was medically excluded	☐
	The participant was unable to physically cooperate	☐
	The participant refused	☐

12. Kodi zinakuchitikirani zoipa zina zirizonse zokhudzana ndi ndondomeko ya ntchito yophweka yopeza ndi kuyang'anila mavuto amapapo pogwiritsa ntchito kupuma pa nthawi yoyeza? Inde ☐
Ayi ☐

Ngati Inde,chonde fotokozani mwa chidule za chochitika chofunikiracho:

_____

_____

_____

13. Ngati otenga nawo mbari anali ndi chochitika choti chikhoza kukhuza zotsatila za ntchito yao yophweka yoyeza ndi kuyang'anila mavuto a mapapo pogwiritsa ntchito kupuma (mwachitsanzo, kyphosis, ziwalo zosowa, etc.) Lembani chochitika apa.

14. Nambala ya ogwira ntchito m'madela

7.3 Appendix C: Published manuscripts

7.3.1 Appendix C1: Cohort profile – Published chapter 2

PLOS ONE

RESEARCH ARTICLE

Cohort profile: The Chikwawa lung health cohort; a population-based observational non-communicable respiratory disease study of adults in Malawi

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Abstract

Purpose

The aim of this article is to provide a detailed description of the Chikwawa lung health cohort which was established in rural Malawi to prospectively determine the prevalence and causes of lung disease amongst the general population of adults living in a low-income rural setting in Sub-Saharan Africa.

Participants

A total of 1481 participants were randomly identified and recruited in 2014 for the baseline study. We collected data on demographic, socio-economic status, respiratory symptoms and potentially relevant exposures such as smoking, household fuels, environmental exposures, occupational history/exposures, dietary intake, healthcare utilization, cost (medication, outpatient visits and inpatient admissions) and productivity losses. Spirometry was performed to assess lung function. At baseline, 56.9% of the participants were female, mean age was 43.8 (SD:17.8) and mean body mass index (BMI) was 21.6 Kg/m^2 (SD: 3.46)

Findings to date

The cohort has reported the prevalence of chronic respiratory symptoms (13.6%, 95% confidence interval [CI], 11.9–15.4), spirometric obstruction (8.7%, 95% CI, 7.0–10.7), and spirometric restriction (34.8%, 95% CI, 31.7–38.0). Additionally, an annual decline in forced expiratory volume in one second [FEV$_1$] of 30.9mL/year (95% CI: 21.6 to 40.1) and forced vital capacity [FVC] by 38.3 mL/year (95% CI: 28.5 to 48.1) has been reported.

collection tools are provided as Supporting Information files. Further information about the data can be obtained from the corresponding author (martin.njoroge@lstmed.ac.uk). All the data from the Chikwawa lung health cohort presented in this article are stored by the research group on safe servers at the Malawi Liverpool Wellcome Trust programme (MLW), Malawi and the BOLD centre at Imperial College London, UK and handled confidentially.

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Competing interests: The authors have declared no competing interests.

Future plans

The ongoing phases of follow-up will determine the annual rate of decline in lung function as measured through spirometry and the development of airflow obstruction and restriction, and relate these to morbidity, mortality and economic cost of airflow obstruction and restriction. Population-based mathematical models will be developed driven by the empirical data from the cohort and national population data for Malawi to assess the effects of interventions and programmes to address the lung burden in Malawi. The present follow-up study started in 2019.

Introduction

Globally, non-communicable respiratory diseases (NCRD) are the third leading cause of non-communicable disease (NCD) mortality, causing an estimated 4 million deaths each year [1]. Amongst the NCRD, asthma and chronic obstructive pulmonary disease (COPD) are the most prevalent, affecting approximately 358 million and 174 million people respectively [2]. Annually, COPD causes 3 million deaths accounting for 6% of all deaths worldwide [2–4]. Furthermore, the deaths from these diseases are rising globally [5] in part due to increased longevity and changes in population structure [6].

The majority of the burden of NCRD mortality and morbidity is in low and middle-income countries (LMIC) [1,7], which now account for 90% of COPD deaths [8]. Several community based studies in LMIC have documented a high prevalence of abnormal lung function, both obstructive and restrictive (low lung volumes) [9–15], whilst several couple have documented low prevalence of COPD [16,17] but high prevalence of respiratory symptoms [17]. In contrast, very few observational cohort studies have reported and described the health and economic burden of NCRD [18,19], especially in LMIC settings. Their prevalence means that there is a pressing need to better document the life course epidemiology and the related health and economic burden of abnormal (obstructive and restrictive) lung function in LMIC [10,11].

Malawi remains one of the poorest countries in the world [20] with 83% of its 18 million inhabitants living in rural areas [21]. With a GDP per capita of $300, over half the households live below the poverty line (using the international poverty line of US$ 1.90 per person per day) [22], and about 50% of the national health expenditure is funded from external donors [23,24]. In common many sub-Saharan African (SSA) countries, Malawi is at the intersection of high rates of communicable respiratory diseases (Tuberculosis (TB), pneumonia), and increasing NCRD [25–27]. Although Malawi has a well-established TB control programme, only 10–20% of patients presenting at primary healthcare facilities with a persistent cough have TB [28]. The prevalence of diagnosed NCRD such as COPD, asthma and pulmonary fibrosis is essentially unknown [29] because lung function testing is not available out with research settings [30]. In Chikwawa where this study is based, lung function testing is not available at primary health facilities or secondary care (Chikwawa District Hospital). There is very limited capacity to perform spirometry in tertiary care, and this is provided by research staff, and for most patients, transport cost would prevent them from travelling to access this.

Recently, however, studies have reported substantial levels of abnormal lung function in Malawi, with spirometric evidence of restrictive and obstructive deficits present in 34.8% (95% CI: 31.7%, 38.0%) and 8.7% (7.0%, 10.7%) of rural adults and 38.6% (34.4%, 42.8%) and 4.2% (2.0%, 6.4%) of urban adults respectively [10,11]. Spirometric deficits were defined according

to the NHANES III Caucasian references [31]. What is not known is, whether, and how these spirometric deficits impact on the everyday lives of the country's people and health system. Potentially, as in other low-income situations, the economic burden of NCRD may have serious adverse outcomes for households including unpredictable household expenditures due to complications and catastrophic health expenditure [32].

To examine the health and economic burden of NCRD, including abnormal lung function in Malawi, our prospective study aims to follow up a population-based cohort of participants in the rural district of Chikwawa, in southern Malawi, who were recruited to a longitudinal follow-up spirometry study conducted between August 2014 and July 2015 (the Chikwawa lung health cohort) [11,15]. The primary objectives of the current study are to; (i) estimate the annualised rate of change in lung function by age and sex as determined by repeating spirometry; (ii) to develop a mathematical population model based on the cohort findings that estimates the life-time health impact of airflow obstruction in Malawian adults in disability-adjusted life years (DALYS); (iii) estimate the health resource use and lifetime costs in the cohort of Malawian adults with airflow obstruction in international dollars (Int$); (iv) produce model estimates of the lifetime cost effectiveness (Int$/DALY) of selected key intervention compared with current practice to define optimum packages of interventions; and (v), recreate these analyses for Malawian adults with low lung volumes. The economic cost will be from a societal perspective and will include health sector costs, patient/family and carer costs and productivity losses [33]. Presently, the Malawian health system recommends the use of salbutamol and beclomethasone inhalers and prednisolone as interventions for chronic asthma management and salbutamol inhalers, prednisolone and hydrocortisone injections as interventions for acute asthma [34] but these interventions are only available in 8% of urban health facilities and 2% of rural health facilities in Malawi [35]. The current study will determine whether the substantial levels of abnormal lung function in Malawian adults are clinically and societally important not only currently, but also in the future by estimating the economic cost of obstructive and restrictive conditions. In addition, the present study will provide a basis for NCRD intervention adoption and implementation within the Malawian health system, society and similar settings.

The aim of this cohort profile paper is to provide a comprehensive description of the Chikwawa lung health cohort as a research resource for potential collaborations, including an overview of the collected data, a description of the baseline characteristics and a summary of the main results published so far.

Cohort description and methods

Setting

The study is currently conducted in Chikwawa district, located in Southern region of Malawi. (see Fig 1).

Study population

The Chikwawa lung health cohort was initiated alongside the Cooking and Pneumonia study (CAPS) [11,36] (Trial registered with ISRCTN, number ISRCTN59448623). CAPS was a cluster randomized trial that investigated the health effects of a cleaner-biomass fuel cookstove intervention [36]. The aim of setting up the Chikwawa lung health cohort was to determine the prevalence and determinates of lung disease amongst adults in Chikwawa, rural Malawi [11]. Since inception, two rounds of follow-up studies have been conducted with the Chikwawa lung health cohort aiming to assess the determinants of lung function trajectories as affected by personal air pollutant exposures, including the CAPS cookstove intervention [15].

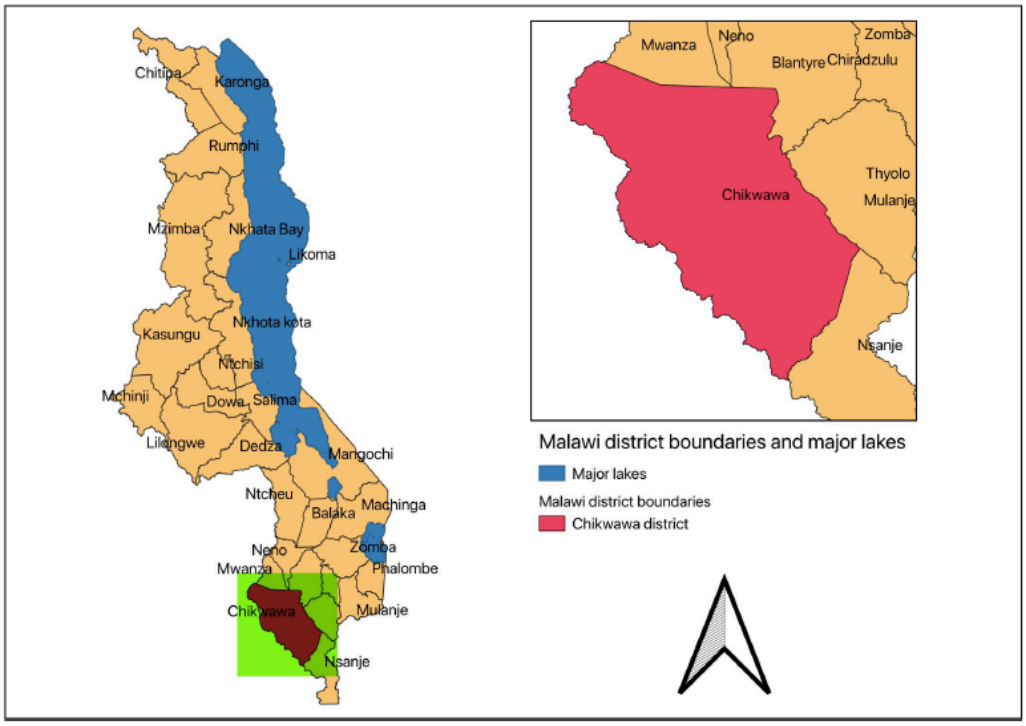

Fig 1. Districts in Malawi. Inset map highlights Chikwawa district, the study area. (Created using the open source QGIS ver. 3.8. Zanzibar (QGIS Development Team, 2020, https://qgis.org.

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The current study will provide additional longitudinal data by further following up participants from the Chikwawa lung health cohort who still reside in Chikwawa and who were recruited to the baseline study in 2014–2015 [11] and quantify associated risk factors, health utilisation use and economic burden.

Statistical analyses

The sociodemographic and clinical variables were determined for the sample using frequencies and proportions for categorical variables and means and standard deviation for continuous variables. Chi-square and t test were used to investigate associations between gender and the other variables.

Baseline participant recruitment

The participants were originally recruited in 2014–2015. The participants were selected through random sampling of a list of adults living in each of the 50 villages participating in CAPS [11]. The participants included those who took part in the CAPS intervention and those who did not but resided in villages where the CAPS intervention was being implemented. The list of adults was obtained from local community liaison personnel from each village following

Table 1. Demographic characteristics of cohort participants.

		Consenting participants n = 1481	Selected, did not give consent n = 1519
Age, mean (SD)		43.9 (17.8)	40.3 (16.5)
Age categories years n (%)	<39	685 (46.3%)	765 (50.3%)
	40–49	258 (17.4%)	336 (22.1%)
	50–59	217 (14.7%)	179 (11.8%)
	60–69	161 (10.9%)	150 (9.9%)
	>70	160 (10.8%)	89 (5.9%)
Sex	Female	844 (57.0%)	757 (49.9%)
	Male	637 (43.0%)	762 (50.2%)

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a series of community engagement events with the village leaders such as chiefs and other community representatives [11]. The random selection was conducted by an independent statistician at the Burden of Obstructive Lung Disease (BOLD) centre in London in accordance with the BOLD protocol [37]. The identified individuals comprised a population-representative, age and gender stratified, sample of adults who were then invited to participate in the 2014–2015 baseline study. Participants had to provide written informed consent or an independently witnessed thumbprint to be included in the study [11]. Those who were acutely unwell or pregnant women or were non-permanent residents of Chikwawa were excluded from the baseline study [11].

A total of 3000 adults were invited to participate in the baseline study of which 1481 (49.3%) agreed to participate [11]. Participants were stratified into two age groups: 18–39 years and 40 years and above. In order to provide an estimate of chronic airflow limitation prevalence in the stratum with a precision (95% CI) of +3.3% to 5.0% and assuming a prevalence of 10% to 25%, a total sample of 1200 participants was estimated allowing for unequal age and gender distribution, refusals and inability to provide spirometry measurements of acceptable quality [11]. Table 1 below summarises the age and sex characteristics of those who agreed to participate in the study compared to those who did not.

Participant tracking and recruitment procedures for the current longitudinal study

In the current study, the adult participants have been tracked from participant logs developed in the original baseline study [11]. The participant log contains the person's name, study identification number, age, gender and village of residence. Community liaison personnel and chiefs were asked to help identify the household of each study participant to maximise fidelity. Study staff then approached the participant in their households, obtained informed consent, geolocation, and agreed a suitable time to collect the lung function, environmental exposures and socioeconomic data.

How often has the cohort been followed up?

Study participants have been followed up twice prior to the current study. The baseline study was conducted between August 2014 –July 2015 [11] with an aim of determining the prevalence and determinates of lung disease. The first and second follow-up studies were between August 2015 –November 2017 [15] aiming to assess the determinants of lung function trajectories as affected by personal air pollutant exposures, including the CAPS cookstove intervention. The current round of follow-up is taking place between July 2019 –March 2021 (see Fig 2).

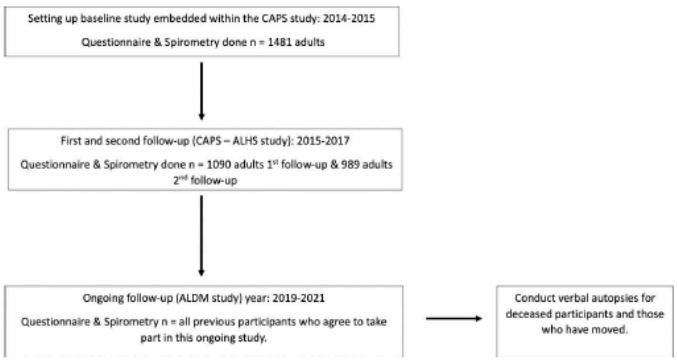

Fig 2. Flow chart of participant recruitment and follow-up schedule.

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Assessment of exposures

In the baseline study, structured interviews were used to collect data on demographic, socio-economic status, respiratory symptoms, and potentially relevant exposures such as smoking [38,39], household fuels [38,40], environmental exposures [39,41], and occupational history [39,42].

In addition to the data collected for the baseline study in the current 2019–2021 follow up, we are collecting additional data on dietary intakes [39,43], healthcare utilization, cost (medication, outpatient visits and inpatient admissions) and productivity losses.

The following anthropometric measures have been recorded at each phase of follow up: height, weight, hip, waist, and neck circumferences, ulna, and fibula lengths. Lung function (forced expiratory volume in one second [FEV_1] and forced vital capacity [FVC]) are measured using the ndd EasyOne Spirometer (ndd Medizintechnik AG, Zurich, Switzerland), before and 15 minutes after administration of inhaled salbutamol (200 μg) administered via spacer device. The contraindications for spirometry include: in the previous three months; thoracic or abdominal surgery, acute coronary syndrome, detached retina or eye surgery; hospitalisation for any other cardiovascular reason in the previous month; final trimester of pregnancy; a resting heart rate > 120 beats per minute and current treatment for tuberculosis [44].

Spirometry has been conducted by trained and certified technicians who received regular feedback on spirogram quality in accordance with the BOLD protocol [37]. The quality of each spirogram has been reviewed and scored based on the American Thoracic Society and European Respiratory Society acceptability and reproducibility criteria [45].

In the current phase of follow-up, verbal autopsies were conducted for the 2014–2015 baseline participants who have died, and a questionnaire was administered to the next of kin for those who were unobtainable due to being no longer resident in Chikwawa. The data and variables collected in the Chikwawa lung health cohort are described in Table 2.

Ethical approval

The study protocol was approved by the Imperial College Research Ethics Committee (17IC4272) (website: https://www.imperial.ac.uk/research-ethics-committee/committees/icrec/), Liverpool School of Tropical Medicine Research Ethics Committee (19–005) (website: https://www.lstmed.ac.uk/research/research-integrity/research-ethics-committee) and the

Table 2. Summary of measurements in the Chikwawa lung health cohort.

Phase	Spirometry measured	Anthropometric measured	Questionnaires & tools administered
Baseline 2014–2015 [11]	• Forced vital capacity (FVC) • Forced expiratory volume in 1 second (FEV_1) • Forced expiratory volume in 6 seconds (FEV_6)	• Weight • Height • Waist & hip circumference	• Socio-economic status • Demographic characteristics • Environmental exposures • Smoking history • History of respiratory disease (Tuberculosis, Asthma and COPD).
First and second follow-up (this follow-up phase was called the CAPS-Adult Lung Health study) 2015–2017 [15]	• FVC • FEV_1 • FEV_6.	• Weight • Height • Waist & hip circumference	• Socio-economic status • Demographic characteristics • Environmental exposures • Smoking history • History of respiratory disease (Tuberculosis, Asthma and COPD). • Personal air pollutant monitoring
Ongoing (this follow-up phase is called Adult Lung Diseases in Malawi study) 2019–2021	• FVC • FEV_1 • FEV_6.	• Weight, • Height; • Ulna & fibula lengths; • Neck, waist & hip circumference.	• Socio-economic status • Demographic characteristics • Environmental exposures • Smoking history • History of respiratory disease (Tuberculosis, Asthma and COPD) • History of health utilization and costs (medication, outpatient & inpatient) • Productivity losses • Household dietary consumption

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Malawi College of Medicine Research and Ethics Committee (COMREC, P.03/19/2617) (website: https://www.medcol.mw/college-of-medicine-research-ethics-committee/). Written informed consent was obtained from all the participants in this study for the follow-up and for the second interview and examination.

Participant and public involvement

Participants were not involved in in setting research questions or the outcome measures but have been instrumental in implementation of the study.

Participants and the public were involved in the dissemination of baseline information nationally through the Ministry of Health, and in the Chikwawa community from which the data was collected through the Chikwakwa Health Research Committee and the Chiefs and community leaders from the villages from where we collected our data. These activities have encouraged community buy-in and involvement in the subsequent rounds of follow-up within the cohort.

Findings to date and discussions

The Chikwawa lung health cohort has provided data characterising the burden of chronic respiratory symptoms, abnormal spirometry and air pollution exposures and risk factors from an adult population in Malawi [11,36]. These data have contributed to the understanding of NCRD in LMIC. The baseline characteristics of the Chikwawa lung health cohort when established in 2014–2015 are outlined in Table 3. At baseline, a total of 1481 participants were recruited of which 637 (43.0%) were male and 844 (57.0%) were female [11]. The mean age was 43.9 years (SD: 17.8), mean body mass index (BMI) was 21.6 Kg/m^2 (SD: 3.46). Cigarette smoking rates were 22.1% (n = 327) were current or ever smokers of which the majority were men (n = 255, 78.0%). There was no difference in ages between the men and women (see Table 3).

Table 3. Baseline demographic, anthropometric and symptomatic characterises of the Chikwawa lung health cohort collected 2014–2015.

Variable (n)		n (%) (total = 1481)	Male n (%) (total = 637)	Female n (%) (total = 844)	P value (X^2)$^{\Psi}$
Age group (years)	<39	685 (46.3%)	288 (45.2%)	397 (47.0%)	0.150
	40–49	258 (17.4%)	103 (16.2%)	162 (18.4%)	
	50–59	217 (14.7%)	110 (17.3%)	110 (12.7%)	
	60–69	161 (10.9%)	70 (11.0%)	96 (10.8%)	
	>70	160 (10.8%)	66 (10.4%)	99 (11.1%)	
BMI ##	Underweight (< 18.5)	182 (13.9%)	84 (13.2%)	98 (11.6%)	<0.001
	Normal weight (≥18.5; <25.0)	950 (72.8%)	465 (73.0%)	485 (57.5%)	
	Overweight (≥25.0; <30.0)	133 (10.2%)	36 (5.7%)	97 (11.5%)	
	Obese (≥ 30.0)	40 (3.1%)	2 (0.3%)	38 (4.5%)	
Smoking	Never	1154 (77.9%)	382 (60.0%)	772 (91.5%)	<0.001
	Current	205 (13.8%)	165 (25.9%)	40 (4.7%)	
	Former	122 (8.2%)	90 (14.1%)	32 (3.8%)	
Symptoms					
Cough on most days of the month for at least three months of the year.		167 (11.3%)	81 (12.7%)	86 (10.2%)	0.148
Usually brings up phlegm from chest		39 (2.6%)	21 (3.3%)	18 (2.1%)	0.221
Wheezing/whistling in chest in the past 12 months in the absence of a cold.		24 (1.6%)	15 (2.4%)	9 (1.1%)	0.082
MRC dyspnoea score II [46,47]: shortness of breath when hurrying on the level or walking up a slight hill.		23 (1.6%)	11 (1.7%)	12 (1.4%)	0.766
Any respiratory symptoms		203 (13.7%)	105 (16.5%)	98 (11.6%)	0.008
Functional limitation: breathing problems interfere with usual daily activities.		44 (3.0%)	21 (3.3%)	23 (2.7%)	0.624
Diagnosed lung disease					
Asthma		51 (3.4%)	23(3.6%)	28 (3.3%)	0.868
Asthma, emphysema, chronic bronchitis, or COPD		59 (4.0%)	28 (4.4%)	31 (3.7%)	0.566
Previous TB		47 (3.2%)	16 (2.5%)	31 (3.7%)	0.268

n = 1341. BMI classification based on WHO guidelines [48].

$^{\Psi}$ Comparison of proportions using Pearson's chi square test.

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The frequency of chronic respiratory symptoms and abnormal spirometry

Among the participants at recruitment in 2014–15, with interpretable and reliable spirometry (n = 886) [37], spirometric obstruction (defined as $FEV_1/FVC < 0.70$) and spirometric restriction (defined as $FEV_1/FVC > 0.70$ and post-bronchodilator $FVC < 80\%$ predicted) [31] were present in 8.7% (95% CI: 7.0%, 10.7%) and 34.8% (95% CI: 31.7%, 38.0%) of the participants respectively according to the NHANES III Caucasian references [11]. 13.7% reported either having a 'cough without having a cold', 'bringing up phlegm from your chest', 'wheezing in your chest', 'shortness of breath when hurrying on the level or walking up a slight hill', or 'breathing problems interfering with your daily activity' while 11.3% reported a 'cough on most days of the month for at least three months per year'. 3.4% were diagnosed with asthma while 4.0% were diagnosed with either asthma, emphysema, chronic bronchitis, or COPD (see Table 3). The 2017 follow-up found that, when compared to the NHANES III African American reference ranges, spirometric obstruction and restriction were present in 11.5% (95% CI: 9.6%, 13.5%) and 7.7% (95% CI: 6.2%, 9.5%) of the participants respectively [15]. For participants who had been followed up in both 2015 to 2017, an overall annual rate of lung function decline in forced expiratory volume in one second [FEV_1] of 30.9mL/year (95% CI: 21.6 to

40.1) and forced vital capacity [FVC] by 38.3 mL/year (95% CI: 28.5 to 48.1) has been reported [15].

Presently, we are able to trace over 85% of the participants in the Chikwawa lung health cohort and have invited them to participate in this current phase of follow-up. The ongoing analysis of the data at a later time point for follow up will provide better estimates for annual rate of lung function decline.

Present research plans

The ongoing current phase of follow-up of the Chikwawa lung health cohort will determine the annual rate of decline in lung function as measured through spirometry, morbidity, mortality and economic cost of airflow obstruction and restriction and develop population-based mathematical models driven by the empirical data from the cohort and national population data for Malawi to assess the effects of interventions and programmes to address the lung burden in Malawi. It is expected that this further phase of follow-up will add to the body of knowledge of the life course of NCRD in LMIC and further refine and add to the validity of the health economic models developed.

Strengths and limitations

The Chikwawa lung health cohort appears to be the only one of its kind in a low-income country setting aiming to investigate the economic costs over the life course of non-communicable respiratory disease. This cohort represents an opportunity to develop and model cost-effective interventions and programmes for this setting. The baseline cohort was conducted alongside a rigorously conducted cluster randomised control trial. Despite local complexities, we presently have identified over 85% of the baseline cohort to be included in the current phase of follow-up.

Systematic bias may be introduced through the self-selection of the participants who agreed to take part in the study to date and the migration of individuals from Chikwawa. Although we have been able to track over 85% of the original Chikwawa lung health cohort and have invited them to participate in the current phase of follow-up, the participants who can be traced and from whom data are collected may differ from those who cannot be traced or do not attend follow-up. Similarly, at baseline, the participants who agreed to be consented were slightly older and mainly women. The process of verbal autopsies for those who have died [49], and collection of data from the next of kin of those who have moved away, may shed some light on the status of those who have moved away from Chikwawa and deaths from respiratory causes will be of particular interest in the current follow-up. The other limitation identified in this study is recall bias. This is due to most of the data being collected through administering questionnaires in a structured interview format, one can expect recall bias over the follow-up period. We are using tested and validated tools in addition to well-trained experienced interviewers to minimize this bias.

The main strength of the cohort is the collection of initial objective measures of lung function using spirometry conducted to internationally agreed standards [37,45] and on two further occasions over a 3-year period. This will provide valuable insights into the health relevance and natural history of abnormal lung functions in an LMIC setting. Previous studies in the United States, the United Kingdom and Australia have reported the annual rate of decline of FEV_1 in adults to be 18 ml/year standard deviation (SD) = 2.5 [50], 33ml/year (SD = 1.5) [51] and 45ml/year (SD = 83) [52].

Supporting information

S1 File. Link to minimal anonymized dataset.
(DOCX)

S2 File.
(PDF)

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7.3.2 Appendix C2: Changing lung function – Published chapter 3

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Changing lung function and associated health-related quality-of-life: A five-year cohort study of Malawian adults

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ABSTRACT

Background: In Sub-Saharan Africa cross-sectional studies report a high prevalence of abnormal lung function indicative of chronic respiratory disease. The natural history and health impact of this abnormal lung function in low-and middle-income countries is largely unknown.
Methods: A cohort of 1481 adults representative of rural Chikwawa in Malawi were recruited in 2014 and followed-up in 2019. Respiratory symptoms and health-related quality of life (HRQoL) were quantified. Lung function was measured by spirometry.
Findings: 1232 (83%) adults participated; spirometry was available for 1082 (73%). Mean (SD) age 49.5 (17.0) years, 278(23%) had ever smoked, and 724 (59%) were women. Forced expiratory volume in one second (FEV_1) declined by 53.4 ml/year (95% CI: 49.0, 57.8) and forced vital capacity (FVC) by 45.2 ml/year (95% CI: 39.2, 50.5) . Chronic airflow obstruction increased from 9.5% (7.6, 11.6%) in 2014 to 17.5% (15.3, 19.9%) in 2019. There was no change in diagnosed asthma or in spirometry consistent with asthma or restriction. Rate of FEV_1 decline was not associated with diagnosed Chronic obstructive pulmonary disease (COPD), asthma, or spirometry consistent with asthma, COPD, or restriction. HRQoL was adversely associated with respiratory symptoms (dyspnoea, wheeze, cough), previous tuberculosis, declining FEV_1 and spirometry consistent with asthma or restriction. These differences exceeded the minimally important difference.
Interpretation: In this cohort, the increasing prevalence of COPD is associated with the high rate of FEV_1 decline and lung function deficits present before recruitment. Respiratory symptoms and sub-optimal lung function are independently associated with reduced HRQoL.

1. Introduction

Chronic obstructive pulmonary disease (COPD) and asthma are the most prevalent chronic respiratory diseases (CRDs) [1]. Globally, COPD accounts for three million deaths annually, 90% of which are in low- and middle-income countries (LMICs) [1,2]. Asthma is the most common CRD, affecting 360 million people, it is the commonest chronic disease of childhood and remains a burden to individuals, their families, and healthcare systems [1]. In LMICs, population-based surveys have reported a high prevalence of respiratory symptoms [3–5], obstructive and restrictive lung function [6,7], but low prevalence of diagnosed COPD [8] suggesting an unrecognised clinical need. International Guideline recommendations are that asthma and COPD require long term treatment and follow-up [9,10]. Knowing the true lifetime CRD burden may potentially have profound implications for provision of respiratory health services. However, given the scarcity of resources competing for healthcare priority there is a pressing need to better document the impact of CRD's on long-term general morbidity. Few studies have reported and described the

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Research in context

Evidence before this study

Multi-national studies report a high prevalence of abnormal lung function in low- and middle-income countries (LMICs) indicative of airflow obstruction (COPD, asthma) and restriction. Very few studies have conducted longitudinal measurement to investigate the natural history of lung function in LMICs and impact on health-related quality of life (HRQoL).

Added value of this study

This study in rural Malawi showed that in a general population of adults, the prevalence of COPD nearly doubled from 9.5% to 17.5% in 5 years. The rate of lung function decline in predominantly non-smoking adults is comparable with that reported for smokers of ≥15 cigarettes a day in high income countries. The respiratory symptoms and reductions in lung function experienced by adult Malawians are associated with clinically significant reductions in HRQoL.

Implications of all the available evidence

The high prevalence of COPD in sub-Saharan Africa adversely affects quality of life and is, in part, a consequence of accelerated lung function decline. The evidence justifies the implementation of sustainable initiatives for widespread diagnosis and management of chronic respiratory diseases in sub-Saharan Africa.

general health impact of diagnosed (and undiagnosed) asthma and COPD in LMICs [11].

In Malawi, two studies have reported significant levels of abnormal lung function with restrictive and obstructive lung function deficits being present in 34.8% (95% CI: 31.7%, 38.0%) and 8.7% (7.0%, 10.7%) of rural adults, respectively, and 38.6% (34.4%, 42.8%) and 4.2% (2.0%, 6.4%) of urban adults, respectively [5,12]. Whether these lung function deficits arise from failure to attain the normal lung function plateau in the third decade and/or from subsequent accelerated decline of lung function remains to be ascertained. In addition, the impact of these lung function deficits on general health status, peoples' everyday lives, and subsequent health service needs, is largely unknown in this and other LMICs settings.

We report here the findings of a cohort study in rural Malawi [3] in terms of annualised rate of change in lung function and associated impact on health-related quality of life (HRQoL) to investigate the natural history of abnormal lung function and its impact on HRQoL in a LMIC.

2. Materials and methods

2.1. Setting and study design

Malawi is one of the world's poorest countries (per capita GDP-$300) and 83% of its 18 million inhabitants live in rural areas [13]. The prevalence of diagnosed COPD and asthma in Malawi is unknown because lung function testing is unavailable out with research settings. Chikwawa (population 360,000) is a predominantly rural district of 4755 km^2 in Southern Malawi.

We report the five year follow-up of a cohort of adult Malawians recruited in 2014. The Chikwawa lung health cohort has been described in detail elsewhere: Njoroge et al. [3]. In 2014 a community-based prevalence survey, nested within a cookstove intervention trial, was conducted in accordance with the Burden of Obstructive Lung Disease (BOLD) protocol [3,14]. Participants were randomly sampled from adults living in 50 villages in Chikwawa: [3,12] of the 3000 invited, 1481 participated. Non-participation was usually because of inability to make contact, non-participants were younger and more likely to be male [3,12].

Two rounds of follow-up in 2015 (n = 1090) and 2017 (n = 989) investigated whether lung function decline was affected by the cook stove intervention or personal air pollution exposures [15]. In 2019, all the participants from 2014 were invited to take part in this five year follow-up.

2.2. Ethical considerations

The study was approved by the Imperial College Research Ethics Committee (17IC4272), Liverpool School of Tropical Medicine Research Ethics Committee (19–005) and the Malawi College of Medicine Research and Ethics Committee (COMREC, P.03/19/2617). All participants provided written informed consent.

2.3. Data collection

Assessments in 2019 were almost identical to those in 2014, 2015 and 2017 and are described in detail elsewhere [3,12,15]. Interviewer administered questionnaires covered respiratory symptoms, smoking history, environmental exposures, demographics, socio-economic status, and diagnosed respiratory disease [3,12].

Lung function (forced expiratory volume in one second [FEV_1] and forced vital capacity [FVC]) was measured by spirometry (NDD Easy-One Spirometer, NDD Medizintechnik AG, Switzerland), performed before and 15 min after 200 μg inhaled salbutamol via spacer. Standard contraindications for spirometry were applied and pregnant women were not tested. The trained and certified spirometry technicians received regular feedback on spirogram quality in accordance with the BOLD protocol [14] and ATS/ERS recommendations [16]. The quality of each spirometry trace was reviewed and scored based on acceptability and repeatability criteria [14,16]. FEV_1 and FVC readings ranked A and B were analysed [16].

The 12–item Short Form Survey (SF–12) (administered in 2014) and the Veterans RAND 12 item survey (VR–12) (administered in 2019) were used to quantify HRQoL from responses to questions on general health perceptions, physical functioning, role limitations due to physical and emotional problems, bodily pain, energy and fatigue, social functioning, and mental health [17,18]. The validated Brazier SF–6D algorithm was applied to obtain a summary preference-based health utility measure (HRQoL utility score) that ranged from 0 (for death) to 1 (full health) [19]. VR–12 responses were mapped to the utility scores from the Brazier SF–6D algorithms to ensure that the scores derived from the SF–12 and VR–12 were comparable. We also assessed the distributional properties of scores obtained from SF–12 and VR–12 tools through the SF–6D algorithms to confirm that they were similar [20,21]. The 2015 and 2017 follow-ups did not include HRQoL.

2.4. Statistical considerations

In 2014, a randomized age, sex-stratified sample was identified from lists of adults living in the 50 cookstove trial villages [3,12]. The baseline sample size estimate of 1200 [3,12], based on the BOLD protocol [14], resulted in a minimum sample size of 300 in any one age/sex stratum (two age groups: 18–39years, ≥ 40years) required to approximate an expected prevalence of fixed airflow obstruction of 10–25% with a precision 3.3–5.0% [12]. To compensate for the cookstove trial's clustered design 1481 participants were recruited.

For the current follow-up, sample size estimates were informed by reported rates of FEV_1 decline in US, UK and Australian cohort

studies [22–24]. We estimated the minimum sample required to detect an annual FEV_1 change ≥ 17 ml to be 146 (73 men, 73 women) per year with 90% power, and $\alpha = 0.05$, and included 10% adjustment for attrition and 20% for important covariates in the analysis. Given the five years between 2014 and 2019, the expected difference would be fivefold, we therefore anticipated a minimum of 730 participants (365 men, 365 women) would suffice.

Global Lung Initiative 2012 reference values for African-American ethnicity were used [25]. Absolute FEV_1 and FVC were included as continuous variables in longitudinal analyses. Each participant's spirometry was categorised into patterns consistent with clinical diagnoses: 'normal,' pre-bronchodilator FEV_1 ≥ lower limit of normal (LLN), FVC ≥ LLN, FEV_1/FVC ≥ LLN; 'COPD,' post-bronchodilator FEV_1/FVC < LLN with no/insignificant bronchodilator reversibility; 'asthma,' pre-bronchodilator FEV_1/FVC < LLN and significant reversibility (post-bronchodilator improvement in FEV_1 ≥ 12% and ≥ 200 ml); and 'restriction,' post-bronchodilator FVC < LLN, FEV_1/FVC ≥ LLN [9,10].

Primary outcome measures were lung function (FEV_1, FVC) and HRQoL score. Rate of change of FEV_1, and FVC were expressed as ml/year and *z*-score/year. Rate of change in HRQoL score associated with changes in the lung function were also estimated. Clinical considerations, analysis of variance and simple linear regression methods identified the following explanatory variables for inclusion in multivariable analysis: follow-up time, age, height, BMI, sex, previous TB diagnosis, smoking, years of schooling, clinical spirometry patterns, reported respiratory diagnoses (any of asthma, emphysema, chronic bronchitis, COPD).

Linear mixed-effects models were used to analyse lung function using all the 2014 and 2019 data. To investigate associations with rates of FEV_1 and FVC, multiplicative terms were individually included in models: time*diagnosed asthma, time*diagnosed COPD, time*previous TB, time*smoking history, time*spirometry consistent with asthma, time*spirometry consistent with COPD, time*restrictive spirometry. Sensitivity analyses included those participants with lung function from both 2014 and 2019. HRQoL data were only collected in 2014 and 2019. Linear mixed-effects models with robust standard errors were used to analyse HRQoL scores because of they have an increasingly skewed distribution. Beta regression models with their important explanatory variables were used to conduct sensitivity analysis of HRQoL to assess validity of the mixed-effects model with robust standard errors. In all mixed-effects models, random effects were accounted for at the individual level whilst the explanatory fixed-effects were selected sequentially with the optimum model fit by likelihood ratio and deviance testing under maximum likelihood estimation. Statistical analysis was conducted using R v3.6.0. All significance tests were two-tailed, with $p < 0.05$ considered significant.

2.5. Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. MWN, PB, GD, AO, LN, and JR had full access to all the data in the study. All the authors had final responsibility for the decision to submit for publication.

3. Results

Between July 2019 and August 2020, 1232 (83%) of the 1481 original participants were assessed. We were unable to follow-up 249: 93 (6.3%) had died, 9 (0.6%) had moved away, 7 (0.5%) were working away, and no information was available for 140 (9.5%). Fig. 1 outlines participant numbers in each follow-up.

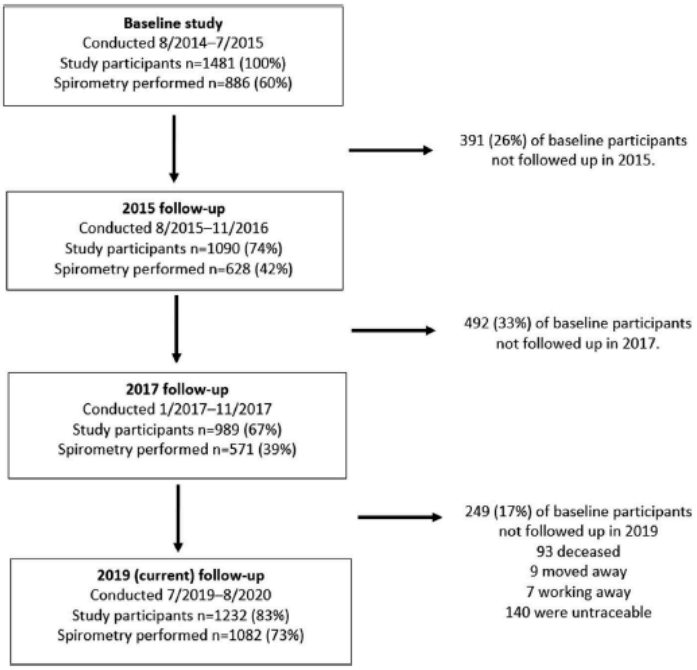

Fig. 1. Participants in the various follow-up phases of the Chikwawa lung health cohort.

Mean (SD) participant age in 2019 was 49.5 (17.0) years, 278 (23%) had ever smoked, and 724 (59%) were women (Table 1). A greater proportion of the 2014 cohort participated in 2019 (n = 1232 (83%)) than in 2015 (n = 1090 (74%)) or 2017 (n = 989 (67%)). Comparison of the 2014 characteristics of those participating or not participating in 2019 (supplement Table E1) indicated that those participating in 2019 were older (mean difference [MD] (95% CI): 7.9 years (5.8, 9.9)), less educated (MD: 1.2 years, 0.7, 1.7), less likely to have acceptable spirometry (percentage difference (95% CI): 12.1% (5.5, 18.7%)), had reduced FEV_1 (MD (95% CI): 3.71%, (0.02, 7.40%)), and reduced HRQoL score (MD (95% CI): 0.03, (0.01, 0.05)). However, participation in 2019 was not significantly associated with sex, smoking history, respiratory symptoms, or diagnoses.

The number of participants providing acceptable spirometry in 2019 (n = 1082) was greater than in 2014 (n = 886), 2015 (n = 628) and 2017 (n = 571), while 675 participants had acceptable spirometry in both 2014 and 2019 (Supplement Table E5). Participants providing acceptable spirometry in 2019 were significantly older, had more years of schooling and were less likely to report coughing, but did not differ significantly for sex, smoking, or symptoms of wheeze, breathlessness or sputum expectoration when compared with participants with no/unacceptable spirometry, (Supplement Table E2).

3.1. Symptoms

There was an increase in reported respiratory symptoms between 2014 and 2019 (Table 2); the proportion difference (95% CI) for 'any respiratory symptom' was 14.7% (11.6, 17.8%); 'cough' 12.5% (9.6, 15.5%); 'sputum expectoration' 7.8% (5.8, 9.7%); 'wheezing' 5.3% (3.7, 7.0%); 'dyspnoea' 4.0% (2.5, 5.6%). Participants also reported more diagnosed asthma, emphysema, or COPD 2.8% (1.0, 4.6%) and previous TB 3.8% (2.1, 5.6%). Restricting analysis to participants providing respiratory symptom data in both 2014 and 2019 made little difference to the magnitude of the observed differences (Supplement Table E3).

Table 1
Characteristics of study participants at baseline (2014) and in 2019.

	Baseline 2014 (n = 1481)	2019 follow-up (n = 1232)
Women, n (%)	844 (57.0%)	724 (58.8%)
Age (years, mean (SD))	43.9 (17.8)	49.5 (17.0)
Grouped age (years), n (%)		
< 39	685 (46.3%)	403 (32.7%)
40–49	258 (17.4%)	268 (21.8%)
50–59	217 (14.7%)	213 (17.3%)
60–69	161 (10.9%)	167 (13.6%)
> 70	160 (10.8%)	181 (14.7%)
BMI (kg/m^2), mean (SD))	21.6 (3.46)	21.8 (3.93)
BMI, n (%)		
Underweight (< 18.5)	182 (13.9%)	219 (17.8%)
Normal weight (≥ 18.5; < 25.0)	950 (72.8%)	795 (64.4%)
Overweight (≥ 25.0; < 30.0)	133 (10.2%)	161 (13.1%)
Obese (≥ 30.0)	40 (3.1%)	58 (4.7%)
Never smoked	1154 (77.9%)	954 (77.4)
Years of schooling completed, mean (SD)	4.21(4.09)	3.80(3.94)
Highest level of education completed		
None	485 (32.7%)	477 (38.7%)
Primary School	758 (51.2%)	576 (46.8%)
High School	232 (15.7%)	165 (13.4%)
College & University	4 (0.27%)	14 (1.14%)
Unknown	2 (0.14%)	0 (0.00%)

Table 2
Changes in symptom prevalence, diagnosed respiratory disease and lung function between 2014 and 2019.

	Baseline 2014 (n = 1481)	2019 follow-up (n = 1232)
Symptoms		
Any respiratory symptoms, n (%)	203 (13.7%)	350 (28.4%)
Cough most days of the month for ≥ 3 months of the year, n (%)	167 (11.3%)	294 (23.8%)
Usually brings up phlegm from chest, n (%)	39 (2.6%)	128 (10.4%)
Wheezing/whistling in chest in the past 12 months, n (%)	63 (4.3%	85 (6.9%)
Wheezing/whistling in chest in the past 12 months in the absence of a cold, n (%)	24 (1.6%)	60 (4.9%)
Shortness of breath when hurrying on the level or walking up a slight hill, n (%)	23 (1.6%)	69 (5.6%)
Breathing problems interfere with usual daily activities, n (%)	44 (3.0%)	44 (3.6%)
Diagnosed lung disease		
Diagnosed asthma, n (%)	51 (3.4%)	56 (4.5%)
Diagnosed COPD, n (%)	1 (0.1%)	11 (0.9%)
Diagnosed asthma, emphysema, chronic bronchitis, or COPD, n (%)	59 (4.0%)	84 (6.8%)
Previous TB, n (%)	47 (3.2%)	87 (7.0%)
Spirometry	*(n = 886)*	*(n = 1082)*
FEV_1 (ml); mean (SD)	2645 (658)	2279 (723)
FVC (ml); mean (SD)	3283 (739)	2983 (835)
FEV_1,%predicted; mean (SD)	97.8% (16.8%)	91.8% (19.3%)
FVC,%predicted; mean (SD)	101% (15.6%)	98.8% (19.8%)
FEV_1/FVC; mean% (SD)	80.5% (8.5%)	76.1% (11.0%)
Obstruction		
FEV_1/FVC < LLN n (%)*	84 (9.5%)	189 (17.5%)
FEV_1/FVC < 0.70 n(%)	82 (9.3%)	232 (21.4%)
Mild: FEV_1 ≥ 80% predicted n (%)	47 (5.3%)	106 (9.8%)
Moderate: 50% ≤ FEV_1 < 80% predicted n (%)	26 (2.9%)	103 (9.5%)
Severe: 30% ≤ FEV_1 < 50% predicted n (%)	8 (0.9%)	17 (1.6%)
Very severe: FEV_1 < 30% predicted	1 (0.1%)	6 (0.6%)
Restriction		
FVC < LLN n (%)	44 (5.0%)	91 (8.4%)
Spirometry clinical pattern		
Normal	702 (79.2%)	748 (68.2%)
COPD*	61 (6.9%)	134 (12.4%)
Asthma	23 (2.6%)	40 (3.7%)
Restriction	34 (3.8%)	52 (4.8%)
Unclassified not normal spirometry pattern	66 (7.4%)	108 (10.0%)

* discrepancy reflect differences numbers for those with acceptable post-bronchodilator spirometry and those with acceptable pre and post bronchodilator spirometry.

3.2. Lung function changes

Comparison of spirometry data between 2014 and 2019 indicated that the unadjusted annual rate of FEV_1 decline was 73.4 ml/year (95% CI): (61.0, 85.6; $p < 0.0001$) and for FVC 60.1 ml/year (46.0, 74.2; $p < 0.0001$) (supplement figure E1). When expressed as percent predicted and z-scores (supplement Table E4), the rate of FEV_1 decline exceeded that of FVC and that predicted by GLI-2012. These rates of decline were reflected in the clinical patterns of lung function such that in 2019 a higher proportion had spirometry consistent with COPD (predominantly mild to moderate), however between 2014 and 2019 there was little difference in the proportion of participants with spirometry consistent with asthma and pure restriction (Table 2).

The lung function characteristics of participants with acceptable spirometry in both 2014 and 2019 ($n = 675$) and for those with data in 2014, 2015, 2017 and 2019 ($n = 276$) are presented in supplementary Tables E5, E6. In the 276 participants with acceptable spirometry in all four study phases, FEV_1 declined by 55.2 ml/year (95% CI: 34.6, 75.8; $p < 0.0001$) and FVC by 47.2 ml/year (22.6, 72.0; $p < 0.0001$).

In the mixed-effects regression model (Table 3) of all participants with acceptable spirometry in 2014 and/or 2019 (model 1), adjusted FEV_1 declined by 53.4 ml/year (95% CI): (49.0, 57.8; $p < 0.0001$) and FVC by 45.2 ml/year (39.2, 50.5; $p < 0.0001$). Reduced FEV_1 and FVC were significantly associated with age (FEV_1 $p < 0.001$; FVC $p < 0.001$), female sex (FEV_1 $p < 0.001$; FVC $p < 0.001$), reducing height (FEV_1 $p < 0.001$; FVC $p < 0.001$), reducing BMI (FEV_1 $p < 0.001$, FVC $p = 0.004$), but not smoking history (FEV_1 $p = 1$; FVC $p = 0.803$) or years of schooling (FEV_1 $p = 1$; FVC $p = 0.251$). Reported previous TB was associated with reduced FEV_1($p < 0.001$) and FVC ($p < 0.001$), whereas reported diagnosed asthma was associated with reduced FEV_1($p = 0.014$) but not FVC($p = 0.453$), a reported diagnosis of emphysema (FEV_1 $p = 1$; FVC $p = 1$), chronic bronchitis (FEV_1 $p = 1$; FVC $p = 1$), or COPD (FEV_1 $p = 0.830$; FVC $p = 0.485$) was not associated with FEV_1 or FVC. When compared to those with normal lung function, spirometry patterns consistent with COPD or restriction were associated with reduced FEV_1($p < 0.001$) and FVC ($p < 0.001$) and spirometry consistent with asthma was associated with reduced FEV_1 ($p < 0.001$) but not FVC ($p = 0.260$). None of the included interaction terms were significantly associated with FEV_1 and FVC indicating that rates of FEV_1 and FVC decline were not associated with diagnosed asthma (FEV_1 $p = 0.429$; FVC $p = 0.619$), previous TB (FEV_1 $p = 0.091$; FVC $p = 0.092$), smoking history (FEV_1 $p = 0.910$; FVC $p = 0.108$), or spirometry consistent with asthma (FEV_1 $p = 0.731$; FVC $p = 0.160$), COPD (FEV_1 $p = 0.900$; FVC $p = 0.977$), or restriction (FEV_1 $p = 0.502$; FVC $p = 0.531$). Inclusion of height squared and cookstove intervention allocation status between 2014 and 2015 in the models revealed no associations between the cookstove intervention or height squared on FEV_1, FVC or their rates of decline. A sensitivity analysis of participants with acceptable spirometry in both 2014 and 2019 (model 2) indicated that adjusted FEV_1 declined by 46.1 ml/year (95% CI): (22.7, 69.0; $p < 0.0001$) and FVC by 42.4 ml/year (37.7, 47.0; $p < 0.0001$). The parameter estimates for FEV_1 and FVC z-scores are presented in supplement Table E7.

3.3. Changes in health-related quality-of-life

Between 2014 and 2019 there was a significant decline in unadjusted mean (SD) HRQoL utility score from 0.873 (0.133) to 0.790

Table 3
Linear Mixed Effects Modelling applied to FEV1 and FVC data from participants in 2014 and 2019, statistically significant associations.

	FEV_1 (ml)		FVC (ml)	
	Model 1[$] Estimate (95% CI)	Model 2[€€] Estimate (95% CI)	Model 1[$] Estimate (95% CI)	Model 2[€€] Estimate (95% CI)
Time to follow-up (per year)	−53.5 (−57.8, −49.0)	−46.1 (−69.0, −22.7)	−45.2 (−50.5, −39.2)	−42.4 (−47.0, −37.7)
Age (per year)	−16.2 (−17.3, −15.0)	−15.6 (−17.0, −13.9)	−10.2 (−11.7, −8.6)	−9.3 (−11.1, −7.3)
Height (per cm)	26.4 (24.0, 29.2)	25.2 (22.2, 28.1)	34.1 (30.6, 37.6)	32.2 (28.3, 36.0)
Sex (female)	−465 (−513, −420)	−488 (−542, −433)	−630 (−686, −569)	−642 (−714, −573)
BMI (per kg/m^2)	12.3 (7.2, 17.3)	12.6 (6.0, 18.1)	9.5 (2.4, 15.8)	8.8 (1.0, 16.5)
Previous TB	−213 (−295, −140)	−198 (−292, −105)	−174 (−276, −84.5)	−189 (−313, −76.1)
Diagnosed asthma	−113 (−196, −32.7)	−123 (−214, −32.7)		
Clinical spirometry pattern (compared to normal)				
COPD	−386 (−428, −346)	−324 (−374, −279)	−146 (−196, −94.4)	−88.9 (−146, −27.9)
Asthma	−627 (−754, −491)	−497 (−669, −312)		
Restriction	−691 (772, −612)	−673 (−773, −753)	−813 (−911, −705)	−754 (−877, −627)

TB, Tuberculosis; BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s.
FEV_1 model: 88% of the variability of FEV_1 accounted for in the final mixed-effects regression model of which fixed-effects accounts for 70% of the variation.
FVC model: 86% of the variability of FVC accounted for in the final mixed-effects regression model of which fixed-effects accounts for 62% of the variation.
[$] Models 1 include FEV_1 and FVC data from all the participants with acceptable spirometry in 2014 ($n = 886$) and/or 2019 ($n = 1082$).
[€€] Models 2, sensitivity analysis, include FEV_1 and FVC data from participants with acceptable spirometry in 2014 and 2019 ($n = 675$).

(0.116) ($p < 0.0001$) and the proportion reporting perfect health (score of 1) declined from 39% ($n = 582$) to 2% ($n = 23$) (Supplement Fig. E2). Reduced HRQoL in 2014 and 2019 was associated with reported respiratory symptoms and previously diagnosed TB (Supplement Table E8). Diagnosed emphysema, chronic bronchitis or COPD was associated with reduced HRQoL in 2019 but not 2014, diagnosed asthma was not associated with HRQoL (Table 4). Spirometry consistent with asthma was associated with reduced HRQoL (MD, (95% CI): 0.080 (0.021, 0.131; $p = 0.0029$), as was spirometry consistent with COPD (0.037, [0.020, 0.055, $p < 0.0001$]) and pure restriction (0.055, [0.020, 0.089, $p = 0.0003$]) (Supplement Fig. E3).

In the mixed-effects regression model (Table 5) reduced HRQoL was associated with time ($p < 0.001$), older age at baseline ($p < 0.001$) and female sex ($p < 0.001$) but not years of schooling ($p = 0.807$) or smoking ($p = 0.085$).

The symptoms of dyspnoea, wheeze, and cough were independently associated with reduced HRQoL, with dyspnoea appearing to be of greatest magnitude and cough the least. Reduced HRQoL was associated with previous TB, but not diagnosed asthma, emphysema, chronic bronchitis, or COPD. HRQoL was beneficially associated with FEV_1%predicted but not FVC. There were no significant interactions between time and diagnosed conditions (diagnosed asthma $p = 0.714$; diagnosed COPD = 0.221; previous TB $p = 0.876$) or spirometric patterns (spirometry consistent with COPD $p = 0.646$; spirometry consistent with asthma $p = 0.409$; spirometry consistent with restriction $p = 0.204$).

4. Discussion

In this first longitudinal study of HRQoL in relation to ventilatory function and chronic respiratory disease in sub-Saharan Africa, we report adjusted annual rates of FEV_1 and FVC decline of 53.4 ml/year and 45.2 ml/year, respectively. More robust estimates of FEV_1 and FVC decline from those participating in both 2012 and 2019 were 46.1 ml/year and 42.4 ml/year, respectively. These rates of decline were reflected in an increase in spirometry consistent with COPD from 9.5% in 2014 to 17.5% in 2019. In the same period diagnosed COPD increased from 0.1 to 0.9%. There was no change in reported diagnosis of asthma or in spirometry consistent with asthma or pure restriction. The second main finding was that HRQoL was adversely and independently associated with the symptoms of dyspnoea, wheeze, and cough, previously diagnosed TB, and declining FEV_1.

The annual rate of FEV_1 decline of 46–53 ml/year in this cohort is greater than the 'normal' 24–29 ml/year decline in healthy non-smokers in high income countries (HICs), but similar to the 40–55 ml/year decline in smokers of ≥ 15 cigarettes/day in HICs, and the 53 ml/year reported in an accelerated FEV_1 decline trajectory group accounting for 48% of COPD in US and European cohorts [22,26]. The cause(s) of the relatively rapid rate of FEV_1 decline in Malawian adults is unclear. Although comparable to smoking 15 cigarettes/day in HICs, smoking is unlikely to underlie the observed decline in the general Malawian because only 14% of participants currently smoked, with most smoking a few cigarettes a day. Previous studies of this cohort have reported no association between lung function (or rate of decline) and smoking status, cookstove intervention and personal pollution exposure ($PM_{2.5}$, CO) [15], similar to the finding from our analysis. The relatively rapid rate of FEV_1 decline may be a result of frequent pulmonary infections consequent upon genetic factors and/or dietary factors. Reduced FEV_1 (but not rate of decline) was associated with diagnosed asthma, previous TB, and spirometry consistent with COPD, asthma, and restriction, suggesting that the differences in lung function had occurred prior cohort set up and were not a consequence of differential rates of FEV_1 decline. This finding is consistent with reports from HICs that reductions in FEV_1 in later adult life observed in COPD and asthma are largely a consequence of the tracking of suboptimal lung function from childhood into adulthood [23,24,27].

The 2015 and 2017 follow-ups of this cohort reported an FEV_1 decline of 30.9 ml/year and for FVC 38.3 ml/year, comparable with rates reported in healthy non-smokers in HICs [15,22,26]. The most likely explanation for the disparity between the 2015/7 and 2019 follow-up (30.9 vs 53.4 ml/year) is the greater number participants with acceptable spirometry in 2019 ($n = 1082$) compared with 2014 ($n = 886$), 2015 ($n = 628$) and 2017 ($n = 571$). It is likely that the

Table 4
HRQoL scores of participants in 2014 and 2019 associations with respiratory symptoms and diagnosed respiratory diseases.

	2014			2019		
	HRQOL scoremean, (SD)			HRQOL scoremean, (SD)		
	Yes	No	p	Yes	No	p
Symptoms						
Any respiratory symptoms	0.805 (0.138) ($n = 203$)	0.894 (0.122) ($n = 1163$)	< 0.001	0.752 (0.133) ($n = 350$)	0.804 (0.100) ($n = 882$)	< 0.001
Cough ≥ 3 months of the year	0.811 (0.141) ($n = 167$)	0.880 (0.130) ($n = 1314$)	< 0.001	0.758 (0.130) ($n = 294$)	0.800 (0.109) ($n = 938$)	< 0.001
Usually brings up phlegm from chest	0.788 (0.153) ($n = 39$)	0.874 (0.132) ($n = 1442$)	0.009	0.731 (0.145) ($n = 128$)	0.796 (0.110) ($n = 1104$)	< 0.001
Wheezing/whistling in chest in the past 12 months, *n* (%)	0.790 (0.147) ($n = 63$)	0.876 (0.131) ($n = 1418$)	< 0.001	0.683 (0.142) ($n = 85$)	0.797 (0.104) ($n = 1147$)	< 0.001
Wheezing in the past 12 months in the absence of a cold	0.789 (0.130) ($n = 24$)	0.874 (0.133) ($n = 1457$)	0.004	0.676 (0.140) ($n = 60$)	0.795 (0.111) ($n = 1172$)	< 0.001
Shortness of breath when hurrying on the level or walking up a slight hill.	0.759 (0.130) ($n = 23$)	0.888 (0.123) ($n = 1310$)	< 0.001	0.687 (0.124) ($n = 69$)	0.796 (0.112) ($n = 1163$)	< 0.001
Breathing problems interfere with usual daily activities.	0.792 (0.151) ($n = 44$)	0.875 (0.132) ($n = 1437$)	0.001	0.669 (0.160) ($n = 44$)	0.794 (0.112) ($n = 1188$)	< 0.001
Diagnosed lung disease						
Diagnosed asthma	0.824 (0.140) ($n = 51$)	0.874 (0.132) ($n = 1430$)	0.014	0.754 (0.149) ($n = 56$)	0.791 (0.114) ($n = 1176$)	0.069
Diagnosed, emphysema, chronic bronchitis, or COPD.	0.827 (0.142) ($n = 59$)	0.874 (0.132) ($n = 1422$)	0.013	0.727 (0.154) ($n = 84$)	0.794 (0.111) ($n = 1148$)	< 0.001
Previous TB	0.806 (0.142) ($n = 47$)	0.875 (0.132) ($n = 1434$)	0.002	0.733 (0.152) ($n = 87$)	0.794 (0.111) ($n = 1145$)	< 0.001

Table 5
Robustly fit linear mixed effects modelling applied to HRQoL data from participants in 2014 and 2019.

	HRQoL[$$]			
	Model A (Symptoms + spirometry clinical pattern)		Model B (Symptoms + spirometry)	
	Estimate(95% CI)	*P* value[Ψ]	Estimate(95% CI)	*p* value[Ψ]
Time to follow-up (2019 vs 2014)[a]	−0.083 (−0.093, −0.073)	< 0.001	−0.081 (−0.091, −0.071)	< 0.001
Age group[b]				
40–49 years	−0.002 (−0.014, 0.011)	0.819	−0.003 (−0.015, 0.010)	0.670
50–59 years	−0.023 (−0.037, −0.009)	0.001	−0.026 (−0.040, −0.011)	< 0.001
60–69 years	−0.020 (−0.036, −0.004)	0.013	−0.022 (−0.038, −0.006)	0.006
≥ 70 years	−0.074 (−0.092, −0.056)	< 0.001	−0.079 (−0.098, −0.060)	< 0.001
Sex (female)	−0.032 (−0.041, −0.022)	< 0.001	−0.031 (−0.041, −0.021)	< 0.001
Symptoms				
Cough ≥ 3 months of the year	−0.023 (−0.037, −0.009)	0.001	−0.023 (−0.037, −0.010)	0.001
Usually brings up phlegm from chest	−0.021 (−0.042, 0.001)	0.058	−0.021 (−0.042, 0.000)	0.047
Wheezing in the past 12 months in the absence of a cold	−0.062 (−0.087, −0.036)	< 0.001	−0.062 (−0.088, −0.036)	< 0.001
Shortness of breath when hurrying on the level or walking up a slight hill	−0.093 (−0.119, −0.066)	< 0.001	−0.091 (−0.117, −0.064)	< 0.001
Diagnoses				
Previous TB	−0.032 (−0.055, −0.009)	0.006	−0.026 (−0.049, −0.003)	0.028
Spirometry pattern[c, &]				
COPD	−0.009 (−0.021, 0.003)	0.152		
Asthma	−0.040 (−0.080, −0.001)	0.047		
Restrictive	−0.037 (−0.059, −0.013)	0.002		
Spirometry				
FEV_1% predicted (per%)			0.0005 (0.000, 0.001)	0.034
FVC% predicted (per%)			0.0004 (−0.0003, 0.001)	0.583

[Ψ] Significance was determined using Satterthwaite approximations of degrees of freedom.
Reference Category.
[a] Baseline study.
[b] < 40 years.
[c] Normal spirometry pattern.
[&] The spirometry pattern variable was added into the model instead of FEV_1 variable.
[$$] Models include HRQoL data from all the participants with acceptable spirometry (2014 *n* = 886, 2019 *n* = 1082).

53.4 ml/year rate of decline reported here is an over-estimate resulting from participants providing spirometry in 2019, but not 2014, who were older, current smokers and symptomatic. The analysis of participants with acceptable spirometry in both 2014 and 2019 supports this notion, even so the rate of FEV_1 decline of 46.1 ml/year is still cause for concern. We did not observe the high rates of restriction reported in urban Malawi (38.6%) and the 2014 baseline study of this cohort (34.8%) [12], probably reflecting use of NHANES III predictive equations for white Americans, whereas we used African-American GLI–2012 predictive equations as recommended by ATS/ERS [16].

Our findings that HRQoL is adversely and independently associated with age, female sex, respiratory symptoms (dyspnoea, wheeze, cough), previous TB and declining FEV_1 is consistent with other studies. A cross-sectional study of 50 Nigerian COPD patients reported that respiratory HRQoL (St Georges Respiratory Questionnaire) is adversely associated with age, female sex and dyspnoea, however the Nigerian study reported no associations with wheeze, cough, or FEV_1, probably reflecting the smaller sample size than our study [28]. The present study differs from a report from BOLD that chronic bronchitis symptoms are associated with reduced HRQoL (SF-12) and the impact is greater than for asthma or COPD [29]. In the current study, dyspnoea and wheeze symptoms were more strongly associated with HRQoL than cough and phlegm symptoms and HRQoL was adversely associated with spirometry consistent with asthma but not COPD. These differences with BOLD may be a consequence of BOLD being of cross-sectional design. Some cross-sectional studies in Africa have reported reduced HRQoL in people with asthma and after TB treatment [30–32]. In the study reported here, a previous diagnosis of TB and spirometry consistent with asthma and wheezing symptoms were adversely associated with HRQoL.

In the current study in Malawi, the differences in HRQoL independently associated with dyspnoea, wheeze, previous TB and spirometry consistent with asthma or pure restriction exceeded the minimally important difference (MID) reported for the SF-6D instrument in longitudinal studies ((MID) (0.033, 95% CI: 0.029–0.037)) and the MIDs reported for SF-6D in people with COPD (0.011, (SD 0.09)) [33].

The present study has strengths and limitations. Strengths include the use of objective validated measures of ventilatory function and HRQoL to follow-up a cohort of adults randomly identified in Malawi. Although this cohort is largely representative of adults in rural Malawi, a limitation is that nonparticipants in the original 2014 study were younger and more likely to be male, anecdotally, younger men

in rural villages are more likely to seek work in towns/cities. The high rate of follow-up of the cohort in 2019 increases confidence in the generalizability of our findings to other similar settings. Spirometry was performed in accordance with ERS/ATS guidelines [16], of high-quality and enabled identification of COPD independent of participant report. Limitations include biases e.g., recall, social desirability, consequent upon reliance on self-reports of symptoms, diagnoses, and exposures by participants. Further limitations include the relatively short 5 year follow-up and unavoidable use of UK tariffs embedded within SF–6D to generate HRQoL scores because appropriate and specific tariffs from relevant sub-Saharan settings have not been published. The choice of tariff does matter, and country-specific tariffs should be used where available. The study was observational and consequently we can only report associations and cannot exclude the possibility of residual confounding by factors associated with participant selection and participation.

In conclusion in this cohort study of adults living in rural Malawi the prevalence of COPD has increased by 1–2% a year and is associated with an annual rate of FEV_1 decline greater than that reported in HICs, combined with lung function deficits present before recruitment that are likely to reflect early life influences and/or sequelae of TB. Respiratory symptom burden and sub-optimal lung function are independently associated with reduced HRQoL of magnitude greater than the minimal important difference. These findings justify further research into the aetiology, natural history, and most importantly sustainable diagnosis and management of chronic respiratory diseases in sub-Saharan Africa.

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Contributors

MWN drafted the study protocol, the first version of the manuscript, conducted the formal analysis and coordinated the present study in Malawi. PM, CC, SR, and RN collected the data for this study. KM, SBG and JB contributed to the set-up of the baseline study. MWN, PB, JR and GD verified the underlying data in this study. AO, LWN, KM and PB acquired the resources for this study. LWN, JR, AO, and GD contributed to the study protocol, formal analysis of this study and contributed to the manuscript in several rounds of review. All authors critically revised the manuscript. All authors read and approved the final manuscript for submission.

Data sharing statement

A minimal anonymised dataset and data collection tools are available online [3]. Further information about the data can be obtained from the corresponding author (martin.njoroge@lstmed.ac.uk). All the data from the Chikwawa lung health cohort presented in this article are stored by the research group on safe servers at the Malawi Liverpool Wellcome Trust programme (MLW), Malawi and the BOLD centre at Imperial College London, UK and handled confidentially.

Declaration of Competing Interest

We declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi: 10.1016/j.eclinm.2021.101166.

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