University of Groningen

Asthma prevalence and mortality in sub Saharan Africa: the case of Uganda

Kirenga, Bruce

DOI:
[10.33612/diss.102038349](https://doi.org/10.33612/diss.102038349)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Kirenga, B. (2019). *Asthma prevalence and mortality in sub Saharan Africa: the case of Uganda*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.
<https://doi.org/10.33612/diss.102038349>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

university of
 groningen

Asthma Prevalence and Mortality in Sub Saharan Africa: The Case of Uganda

PhD thesis

to obtain the degree of PhD at the
University of Groningen
on the authority of the
Rector Magnificus Prof. C. Wijmenga
and in accordance with
the decision by the College of Deans.

This thesis will be defended in public on

Wednesday 27th November 2019 at 11.00 hrs

by

Bruce James Kirenga

born on 12 January 1975
in Kiboga, Uganda

Promotores

Prof. dr. T. van der Molen

Prof. dr. H.M. Boezen

Prof. dr. M.R. Kamya

Co-promotor

Dr. C. de Jong

Assessment Committee

Prof. dr. M.J. Postma

Prof. dr. H.A.M. Kerstjens

Prof. dr. P.J. Sterk

Paranymphs

Job van Boven
Edgar Twine

Table of Contents

CHAPTER 1: GENERAL INTRODUCTION	1
1.1 Definition of asthma	1
1.2 The burden of asthma	1
1.3 Factors associated with the development of asthma	1
1.4 Pathogenesis of asthma	2
1.5 Asthma case definition	3
1.6 Uganda	5
1.7 Objectives and rationale for this thesis	6
References	8
CHAPTER 2: Prevalence and factors associated with asthma among adolescents and adults in Uganda: a general population-based survey	12
ABSTRACT	13
2.1 BACKGROUND	14
2.2 METHODS	14
2.3 RESULTS	17
2.4 DISCUSSION	22
2.5 CONCLUSION	23
References	25
2.6 ADDITIONAL FILES	27
2.7 Supplementary tables	27
CHAPTER 3: The proportion of asthma and patterns of asthma medications prescriptions among adult patients in the chest, accident and emergency units of a tertiary health care facility in Uganda	31
ABSTRACT	32
3.1 INTRODUCTION	33
3.2 METHODS	33
3.3 RESULTS	35
3.4 DISCUSSION	36
References	38
CHAPTER 4: Chronic respiratory diseases in a tertiary health care facility in a developing country in Africa: a hospital based descriptive study	40
ABSTRACT	41
4.1 BACKGROUND	42
4.2 METHODS	42
4.3 RESULTS	43
4.4 DISCUSSION	44
References	46

CHAPTER 5: Rates of asthma exacerbations and mortality and associated factors in Uganda: a 2-year prospective cohort study	47
ABSTRACT	48
5.1 BACKGROUND	49
5.2 METHODS	49
5.3 RESULTS	50
5.4 DISCUSSION	52
5.5 Online supplemental material for the manuscript “Rates of asthma exacerbations and mortality and associated factors in Uganda: a 2-year prospective cohort study.”	55
5.5.1 METHODS	56
5.5.2 RESULTS	58
References	62
CHAPTER 6: The impact of HIV on the prevalence of asthma in Uganda: a general population survey	63
ABSTRACT	64
6.1: BACKGROUND	65
6.2 METHODS	66
6.3 RESULTS	67
6.4 DISCUSSION	71
References	74
CHAPTER 7: The State of Ambient Air Quality in Two Ugandan Cities: A Pilot Cross-Sectional Spatial Assessment	77
ABSTRACT	78
7.1 INTRODUCTION	79
7.2 METHODS	80
7.2.1 Study Design	80
7.2.2 Study Sites and Monitoring Approaches	80
7.2.3 Air Pollutant Sampling Methods	82
7.2.4 Meteorological Measurements	82
7.2.5 Data Analysis	82
7.2.6 Ethics Approval	82
7.3 RESULTS	83
7.3.1 Temperature and Humidity	83
7.3.2 PM _{2.5}	83
7.3.4 Gas Phase Pollutants	85
7.3.5 Nitrogen Dioxide	85
7.3.6 Sulfur Dioxide	85
7.3.7. Ozone	86

7.4 DISCUSSION	86
7.5 CONCLUSIONS	88
7.6 REFERENCES and NOTES	89
7.7 Supplementary Tables	91
CHAPTER 8: Lung Function of Children at Three Sites of Varying Ambient Air Pollution Levels in Uganda: A Cross Sectional Comparative Study	94
ABSTRACT	95
8.1 INTRODUCTION	96
8.2 MATERIALS AND METHODS	96
8.2.1 Sample Size	97
8.2.2 Recruitment	97
8.2.3. Data collection/Procedures	97
8.2.4. Data Analysis.	98
8.2.5. Ethical Considerations.	99
8.3 RESULTS	99
8. 3.1. Study Participants Characteristics	99
8. 3.2. Air Pollution	100
8.3.3. Lung Function	101
8.3.4. Factors Associated with Lung Function	103
4. DISCUSSION	104
5. CONCLUSIONS	107
References	108
CHAPTER 9: GENERAL DISCUSSION	112
9.1 Summary of main findings	112
9.2 Interpretation	113
9.3 Strengths of the studies	115
9.4 Limitations of the studies	116
9.5 Overall conclusion	116
9.6 Recommendations	116
References	120
CHAPTER 10: SUMMARY	122
ACKNOWLEDGEMENTS	124
CURRICULUM VITAE	125
LIST OF PUBLICATIONS	126

CHAPTER 1: GENERAL INTRODUCTION

1.1 Definition of asthma

The Global Initiative for Asthma (GINA) defines asthma as a heterogeneous disease usually characterized by chronic airway inflammation and accompanied by history of recurrent or persistent respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable airflow obstruction.¹ The variation in symptoms and airflow obstruction can in most cases be associated with an identifiable trigger such as allergen exposure, exercise, change in weather or chest infection.^{2, 3} Symptoms can be absent for several weeks or months following appropriate asthma treatment or even spontaneously, a phenomenon that makes the diagnosis of asthma very difficult.^{2, 3}

1.2 The burden of asthma

Asthma is estimated to affect 334 million people globally.⁴ Although the lack of a universally acceptable definition of asthma for use in epidemiological studies makes reliable comparison of asthma prevalence between countries difficult, it is estimated that the prevalence of asthma ranges between 1-16% globally.⁵ The prevalence of asthma is decreasing in developed western countries, but is reported to be increasing in most low and middle income countries (LMIC).⁶⁻⁸ In Africa for example the number of people suffering from asthma increased from 74.4 million in 1990 to 119.3 million in 2010 according to one systematic review.⁷ The increasing prevalence of asthma in LMIC has been attributed to various factors including urbanization, increasing exposure to environmental risk factors and adoption of westernized affluent lifestyles.^{7, 9} In 2016, 420,000 people were estimated to have died from asthma worldwide, giving an age standardized death rate of 6.3 per 100,000.¹² Although the asthma mortality rate reported in 2016 is 24.3% lower than that reported in 2006, asthma mortality rates are increasing in most LMIC especially those in Africa.^{8, 12, 13}

Figure 1.1. Worldwide prevalence of wheezing asthma, from To T et al.⁵

1.3 Factors associated with the development of asthma

Asthma develops from the interaction of host susceptibility factors and environmental factors. Host factors include genetics, obesity, sex, prematurity and low birth weight among others. Environmental

factors notorious for causing asthma include exposure to allergens, occupational sensitizers, respiratory infections, tobacco smoke exposure, indoor and outdoor air pollution, the microbiome, certain diets, pre and perinatal factors and certain medications. Twin studies demonstrate that the inheritability of asthma is in the range of 25-80%, but the heritability in asthma does not follow the simple Mendelian pattern that is seen in monogenic (or single gene) disorders such as cystic fibrosis.¹⁴ Over 100 genes have been implicated in the development of asthma and gene environment interaction also play a role.¹⁵⁻¹⁹ However, none of these, alone or in combination, has been found sufficient to be a sufficient cause for asthma.

Exposure to indoor and outdoor allergens is probably the most studied environmental risk factor for asthma. Indoor allergens such as house dust mites, furred animals such as dogs and cats, cockroaches, fungi, molds and yeasts play a significant role in asthma development in children.²⁰ In LMIC, indoor and outdoor air pollution are increasingly being associated with asthma. Globally about 3 billion people (the majority from LMIC) depend on biomass fuels for cooking, lighting and heating used indoors in poorly ventilated places. At the same time, levels of ambient air pollution are very high especially in LMIC where 97% of cities do not meet WHO air quality standards. Several studies have found a strong association between indoor and outdoor air pollution and asthma.²³⁻²⁹ Closely related to air pollution is urbanization which has been associated with asthma in several studies including those in Uganda.³⁰ ³¹It is therefore likely that air pollution is a key driver of the increasing prevalence of asthma in LMIC.

Another key factor associated with asthma is the occurrence of respiratory infections.^{32, 33} The most commonly implicated viral infection especially in children is the respiratory syncytial virus (RSV) ³³ and among bacteria, *Mycoplasma pneumoniae* is commonly encountered in asthma exacerbations. ³², ³³ In LMIC, infections such as human immunodeficiency virus (HIV) and tuberculosis (TB) are being increasingly reported to be associated with asthma.³⁴⁻³⁶ Given the high burden of HIV and TB in Africa, these infections could be one of the key drivers of the increasing prevalence of asthma in Africa.

1.4 Pathogenesis of asthma

The common pathological pathway in asthma is airway inflammation. Multiple cells are involved in airway inflammation in asthma. Mast cells produce the bronchoconstrictor histamine and other mediators such as prostaglandin D2, and cysteinyl leukotrienes (LTC4, D4, and E4). These mediators cause airway smooth muscle contraction and stimulate reflex neural pathways which are key in the early phase reaction in the case of allergic asthma.^{38, 39} Eosinophils produce basic proteins and cysteinyl leukotrienes which damage airway epithelial cells, T lymphocytes release specific cytokines such as interleukin-4 (IL-4), IL-5, IL-9 and IL-13. which potentiate eosinophilic inflammation, dendritic cells mobilize allergens from the airway surface into regional lymph nodes where they interact with regulatory T cells to produce T cells from naïve T cells. Subsequently, T cells participate in production of more inflammatory cytokines and macrophages interact with allergens to produce inflammatory mediators and neutrophils which are believed to cause airway inflammation through such mediators as matrix metalloproteinase-9 (MMP-9), neutrophil elastase (NE), and IL-8.⁴⁰

Structural cells of the airways have also been found to participate in the production of mediators of airway inflammation. For example, airway epithelial cells produce inflammatory proteins, cytokines and chemokines in response to mechanical changes in their environment such as presence of air

pollutants and bacteria and viruses. Airway smooth muscle undergo hyperplasia and hypertrophy and produce cytokines and chemokines while endothelial cells of the bronchial circulation show increased recruitment of inflammatory cells to sites of injury in asthma. Fibroblasts and myofibroblasts show increased production of connective components such collagen and airway nerves show heightened response which result into bronchoconstriction and mucus secretion.

The wide range of cells involved in asthma and their unique inflammatory pathways is probably one of the reasons that have precluded the finding of universally effective asthma specific therapies.⁴¹

Airway inflammation leads to two physiological changes in the airways- bronchoconstriction and bronchial hyperresponsiveness (BHR). Bronchoconstriction is believed to be caused by airway smooth muscle contraction in response to bronchoconstrictor mediators, airway edema due to increased microvascular leakage in response to inflammatory mediators, airway thickening and mucus hypersecretion. BHR is a lower propensity to airway narrowing upon exposure to a stimulus that would be innocuous in a healthy person. The mechanisms through which inflammation causes BHR are incompletely understood but excessive contraction of airway smooth muscles, uncoupling of airway contraction, thickening of the airway wall and sensitization of sensory nerves within the airways are some of the commonly cited mechanisms.^{41, 42}

1.5 Asthma case definition

Asthma presents with respiratory symptoms such as wheezing, shortness of breath, chest tightness and cough and expiratory airflow limitation. The listed respiratory symptoms and expiratory airflow limitation occur in many other respiratory diseases making the diagnosis difficult. Most asthma patients however show a large variability in symptoms and measurements of lung function. For these symptoms and the airflow limitation to point to asthma they must be variable. Variability of expiratory flow limitation in asthma is present when there is excessive variability in lung function in the presence of documented airflow limitation (reduced FEV_1/FVC ratio i.e. FEV_1/FVC ratio < 0.70 or $<$ lower limit of normal [LLN]).^{43, 44}

Variable expiratory airflow is defined as an increase in FEV_1 of 12 percent or more, accompanied by an absolute increase in FEV_1 of at least 15 minutes after administration of 400 μ g of inhaled salbutamol.⁴³ Other means of assessing replace with variable expiratory airflow include: excessive variability in twice daily peak expiratory flow (PEF) rate over two weeks defined as an average daily diurnal PEF variability of $>10\%$ in adults and 13% in children, significant increase in lung function after 4 weeks of anti-inflammatory treatment defined by an increase in FEV_1 of 12 percent or more, accompanied by an absolute increase in FEV_1 of at least 200 mL or increase in PEF of $>20\%$ from baseline after anti-inflammatory treatment, positive exercise challenge defined as a fall in FEV_1 of $>10\%$ and 200ml in adults from baseline and positive bronchial provocation tests which is defined as fall in FEV_1 of $\geq 20\%$ with standard doses of methacholine or histamine.^{43, 45}

Other clinical features and tests can support the diagnosis. The clinical features that support the diagnosis of asthma include personal or family history of asthma, allergies, use of asthma medication with improvement and a physical examination that reveals an expiratory wheeze (rhonchi) or even a silent chest in severe forms of asthma. The tests that support a diagnosis of asthma include allergy

tests, exhaled nitric oxide, raised peripheral blood and sputum eosinophil count. Of note, these tests are increasingly being seen as means of asthma phenotyping rather than means of asthma diagnosis.⁴⁶

The differential diagnoses of asthma are many although some could be regarded as comorbidities rather than differential diagnoses. In children, chronic upper airway cough syndrome, foreign body and several inborn respiratory conditions such as cystic fibrosis, primary ciliary dyskinesia can occur. Heart diseases, including congenital heart diseases are also a differential diagnosis. In adolescents and young adults, vocal cord dysfunction, dysfunctional breathing and hyperventilation syndromes, bronchiectasis and chronic heart diseases are common differential diagnoses while in the middle aged and the elderly chronic heart failure, chronic obstructive pulmonary disease (COPD), pulmonary embolism, bronchiectasis and interstitial lung diseases are commonly encountered. Asthma is also usually associated with comorbidities that must be appreciated and considered while making a diagnosis of asthma. Commonly encountered comorbid conditions in asthma include depression, allergic rhinitis, gastroesophageal disease, obstructive sleep apnea, and obesity.⁴⁷

Making a diagnosis of asthma is challenging, especially in surveys, because of the lack of a clear case definition. In surveys, operational definitions of asthma have been used.^{4, 49} Most of the operational definitions are based on asthma symptoms, life time asthma symptoms, previous use of asthma medications and physician diagnosis of asthma.⁴⁹ The estimates of asthma obtained by these different criteria can vary, making comparisons of asthma prevalence across countries difficult. Sá-Sousa et al have conducted a systematic review of the different operation definitions used in surveys and applied the most frequently used to classify asthma in two asthma survey databases, the Portuguese National Asthma survey (INAsma) and the 2005–2006 National Health and Nutrition Examination Survey (NHANES).⁵⁰ By applying these definitions of current asthma on INAsma and NHANES data, the prevalence ranged between 5.3%-24.4% and 1.1%-17.2%, respectively.⁵⁰ Daines et al have performed a systematic review of clinical prediction models used to support asthma diagnosis in primary care.⁵¹ They found that all available models have a high risk of bias and are unreliable.⁵¹ There are also efforts to determine a comprehensive asthma score that combines several asthma symptoms and characteristics, but none of these has been widely accepted.⁵²

The challenge of arriving at an accurate asthma diagnosis is much bigger in LMIC where clinical expertise and equipment and diagnostic tests are scarce. There is a published guidance for asthma diagnosis and management based on local expertise and available resources for LMIC.⁵³ In this guidance, it is recommended that clinicians are confident in arriving at a clinical diagnosis of asthma. The guidance is tailored to helping clinicians make a diagnosis of asthma in clinical settings and is unsuitable for use in surveys. For surveys, until better case definitions are found, existing survey questionnaires will remain the best available tools for diagnosis of asthma in population-based surveys.

1.6 Uganda

Figure 1.11 Map showing position of Uganda in East Africa and Africa. https://ichef.bbci.co.uk/news/304/media/images/87716000/gif/_87716346_7d541678-610c-4f7c-95d2-ee872aae5dec.gif

The studies in this thesis were conducted in Uganda. Uganda is a land locked country located in East Africa, bordered by South Sudan in the north, Kenya in the east, Tanzania and Rwanda in the south and Democratic Republic of Congo in the West.⁵⁵ The capital city of Uganda is Kampala. Uganda is situated between latitude 4° 12' N and 1° 29' S and longitudes 29° 34' and 35° 0' E with a total surface area of 241,038km².⁵⁵

The 2014 national census estimated the population of Uganda to be 34.9 million people, although more recent estimates puts the population at 45.7 million.^{57, 58} About half of the population is below 15 years and 82 percent of the population lives in rural areas while 18 percent live in urban areas.⁵⁸ The proportion of males to females is 1:1 and life expectancy is estimated at 60 years for males and 65 years for females.⁵⁷ The fertility rate is 5.9 children per woman and the probability of dying under five years is 49/1000 live births and that of dying between 15 and 60 years is 333/1000 population for males and 243/1000 population for females.^{54, 57}

The official language is English although there are up to 53 dialects spoken by the 53 tribes that constitute Uganda.⁵⁶ Uganda's climate is typically tropical with two rainy and two dry seasons.⁵⁶ Uganda is a low-income country with a gross national income (GNI) of US\$ 1370 and gross domestic product (GDP) of US\$ 27,465 million in 2014.⁵⁷ Total expenditure on health per capita was US \$133 in 2014 and the expenditure on health as % of the GDP was 7.2 in 2014.^{57, 59}

Health care delivery in Uganda is organized as shown in Figure 1.2 and guided by the national health sector development plan (HSDP).⁶⁰ Health care delivery is shared between the public sector and the private sector. The latter is divided into private health providers, private Not for Profit (majority of which are faith based) and traditional or complimentary medicine practitioners. The public health sector starts with national referral hospitals and cascades down into smaller units- regional referral hospitals, general hospitals, health centres (HC) IV, HCIII, HCII and finally the village health team (VHT). The population sizes estimated to be served at each of these levels are shown in Figure 1.2.

Figure 1.2 Structure of the health system in Uganda: https://www.researchgate.net/profile/Susan_Welburn/publication/303423939/figure/fig1/AS:371186543415296@1465509176819/Structure-of-the-health-system-in-Uganda.png

Asthma care is provided at all health care delivery systems levels; at national referral hospitals asthma care is provided in specialized chest clinics and pulmonary wards. In general hospitals, asthma care is provided in medical outpatients' clinics and medical wards and in HCIV-II asthma care is provided in general outpatients' clinics and wards. Within the Ministry of Health, the organization of asthma care in terms of policy and guidelines and supervision is the responsibility of the non-communicable diseases (NCD) department.

1.7 Objectives and rationale for this thesis

The main scientific objective of the studies presented in this thesis is to determine asthma prevalence, the factors associated with asthma, asthma morbidity and mortality in Sub Saharan Africa (SSA) with a focus on Uganda. Data on the prevalence, risk factors and burden of asthma in Africa is severely limited especially for Uganda where until the studies in this thesis were published, there was no published report on the prevalence and burden of asthma. To achieve our objectives, we conducted a national

population survey to determine the prevalence and factors associated with asthma at population level. In addition, we conducted hospital-based surveys to determine the prevalence of asthma among inpatients and outpatients in Mulago National referral hospital, the largest hospital in East Africa. To determine the morbidity and mortality associated with asthma we conducted a two-year prospective cohort study of asthma patients to document the incidence of asthma exacerbations and mortality and their predictors. To understand the role of air pollution and HIV as key factors commonly associated with asthma in LMIC 3 additional studies were conducted. A cross sectional survey of air pollution levels in the two largest cities in Uganda followed by a comparative survey of the lung function and lung health of children in the polluted cities. For HIV we analyzed for the effect of HIV on asthma prevalence in the national asthma survey above. The detailed methods and findings from these studies are presented in chapter 2 to 8 of this thesis.

In **Chapter 2** the aim was estimating the national asthma prevalence in Uganda. The large sample size of this survey allowed analysis for known risk factors for asthma and risk factors specific for sub Saharan Africa (SSA) such as HIV, tuberculosis (TB) and biomass smoke exposure. The large sample size also allowed us to conduct subgroup analyses by gender, age groups and asthma screening questions (physician diagnosis, use of asthma medications and current wheeze and wheeze in the past 12 months).

Chapter 3 presents results from a survey of asthma in an outpatient setting in Uganda (the chest clinic and accident and emergency department, Mulago national referral hospital). The objective of this study was to determine the proportion of adult patients diagnosed with asthma and the proportion of asthma patients that received recommended asthma therapy according to GINA guidelines over a one-year period. The longitudinal nature of this study (although retrospective) also allowed us to analyze for the role of seasonality in asthma health care utilization in Uganda.

Chapter 4 provides data on asthma in an inpatient setting (the pulmonology unit of Mulago national referral hospital). This study aimed to determine the proportion, mortality, and average length of stay of patients with asthma and other chronic respiratory diseases in a tertiary healthcare facility in Uganda. Because this study included data on other chronic respiratory diseases, it provided some insight into the relative importance of the burden of asthma compared to other respiratory diseases encountered in health facilities in Uganda.

Chapter 5 builds on the findings of the retrospective analysis in chapter 3 & 4 by discussing data on asthma morbidity and mortality in a larger prospective cohort study. The objective of this study was to determine the rates of asthma exacerbations and mortality and associated factors. We also collected medication use data as well as causes of death in this study which we could not get in the retrospective chart reviews.

Chapter 6, 7 and 8 provide detailed data on air pollution and HIV and their impact on asthma and respiratory symptoms. Chapter 6 covers the impact of HIV on asthma prevalence at population level. In chapter 7, we present findings from a survey on levels of air pollutants in two large cities in Uganda-Kampala and Jinja. Chapter 8 builds on chapter 7 by presenting results from a survey of children's lung health in polluted cities and a comparator rural site.

References

1. 2019 GINA Report, Global Strategy for Asthma Management and Prevention Available: <https://ginasthma.org/pocket-guide-for-asthma-management-and-prevention/>. Accessed May 27, 2019.
2. Vernon MK, Wiklund I, Bell JA, et al. What do we know about asthma triggers? A review of the literature. *Journal of Asthma*. 2012;49(10):991-998.
3. Gautier C, Charpin D. Environmental triggers and avoidance in the management of asthma. *Journal of asthma and allergy*. 2017;10:47.
4. To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC public health*. 2012;12(1):204.
5. Lai CK, Beasley R, Crane J, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*. 2009;64(6):476-483.
6. Pearce N, Ait-Khaled N, Beasley R, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*. 2007;62(9):758-766.
7. Adeloye D, Chan KY, Rudan I, et al. An estimate of asthma prevalence in Africa: a systematic analysis. *Croatian medical journal*. 2013;54(6):519-531.
8. Kwizera R, Musaaizi J, Meya DB, et al. Burden of fungal asthma in Africa: A systematic review and meta-analysis. *PloS one*. 2019;14(5):e0216568.
9. Weinberg EG. Urbanization and childhood asthma: an African perspective. *Journal of allergy and clinical immunology*. 2000;105(2):224-231.
10. Vos T, Abajobir AA, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*. 2017;390(10100):1211-1259.
11. Hay SI, Abajobir AA, Abate KH, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*. 2017;390(10100):1260-1344.
12. Naghavi M, Abajobir AA, Abbafati C, et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*. 2017;390(10100):1151-1210.
13. Kirenga BJ, de Jong C, Mugenyi L, et al. Rates of asthma exacerbations and mortality and associated factors in Uganda: a 2-year prospective cohort study. *Thorax*. 2018;73(10):983-985.
14. Vercelli D. Discovering susceptibility genes for asthma and allergy. *Nature reviews immunology*. 2008;8(3):169.
15. Demenais F, Margaritte-Jeannin P, Barnes KC, et al. Multiancestry association study identifies new asthma risk loci that colocalize with immune-cell enhancer marks. *Nature genetics*. 2018;50(1):42.
16. Hsu C-L, Neilsen CV, Bryce PJ. IL-33 is produced by mast cells and regulates IgE-dependent inflammation. *PloS one*. 2010;5(8):e11944.

17. Moffatt MF, Kabesch M, Liang L, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature*. 2007;448(7152):470.
18. Duffy DL, Martin NG, Battistutta D, et al. Genetics of Asthma and Hay Fever in Australian Twins1-3. *Am rev respir Dis*. 1990;142:1351-1358.
19. Van Eerdewegh P, Little RD, Dupuis J, et al. Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. *Nature*. 2002;418(6896):426.
20. Brussee JE, Smit HA, van Strien RT, et al. Allergen exposure in infancy and the development of sensitization, wheeze, and asthma at 4 years. *Journal of allergy and clinical immunology*. 2005;115(5):946-952.
21. Household air pollution and health Available: <https://www.who.int/news-room/fact-sheets/detail/household-air-pollution-and-health>. Accessed March 7, 2019.
22. WHO Global Ambient Air Quality Database (update 2018) Available: <https://www.who.int/airpollution/data/cities/en/>. Accessed March 7, 2019.
23. Dockery DW, Speizer FE, Stram DO, et al. Effects of Inhalable Particles on Respiratory Health of Children1-4. *Am rev respir Dis*. 1989;139:587-594.
24. Bowatte G, Lodge C, Lowe AJ, et al. The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization: a systematic review and a meta-analysis of birth cohort studies. *Allergy*. 2015;70(3):245-256.
25. Von Mutius E, Martinez FD, Fritzsch C, et al. Prevalence of asthma and atopy in two areas of West and East Germany. *American journal of respiratory and critical care medicine*. 1994;149(2):358-364.
26. Oluwole O, Arinola GO, Huo D, et al. Biomass fuel exposure and asthma symptoms among rural school children in Nigeria. *Journal of Asthma*. 2017;54(4):347-356.
27. Trevor J, Antony V, Jindal SK. The effect of biomass fuel exposure on the prevalence of asthma in adults in India—review of current evidence. *Journal of Asthma*. 2014;51(2):136-141.
28. Ocakli B, Acarturk E, Aksoy E, et al. The impact of exposure to biomass smoke versus cigarette smoke on inflammatory markers and pulmonary function parameters in patients with chronic respiratory failure. *International journal of chronic obstructive pulmonary disease*. 2018;13:1261.
29. Cai Y, Zijlema WL, Doiron D, et al. Ambient air pollution, traffic noise and adult asthma prevalence: a BioSHaRE approach. *European Respiratory Journal*. 2017;49(1):1502127.
30. Morgan BW, Siddharthan T, Grigsby MR, et al. Asthma and allergic disorders in Uganda: a population-based study across urban and rural settings. *The Journal of Allergy and Clinical Immunology: In Practice*. 2018;6(5):1580-1587. e1582.
31. Siddharthan T, Grigsby M, Morgan B, et al. Prevalence of chronic respiratory disease in urban and rural Uganda. *Bulletin of the World Health Organization*. 2019;97(5).
32. Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. *Bmj*. 1993;307(6910):982-986.
33. Yeh J-J, Wang Y-C, Hsu W-H, et al. Incident asthma and *Mycoplasma pneumoniae*: A nationwide cohort study. *Journal of allergy and clinical immunology*. 2016;137(4):1017-1023. e1016.
34. Ganderia B. The association between asthma and tuberculosis. *Journal of Allergy*. 1962;33(2):112-129.
35. Karahyla JK, Garg K, Garg RK, et al. Tuberculosis and Bronchial Asthma: Not an Uncommon Association.

Chest. 2010;138(4):670A.

36. Kirenga BJ, de Jong C, Katagira W, et al. Prevalence and factors associated with asthma among adolescents and adults in Uganda: a general population based survey. *BMC public health*. 2019;19(1):227.
37. von Mutius E, Pearce N, Beasley R, et al. International patterns of tuberculosis and the prevalence of symptoms of asthma, rhinitis, and eczema. *Thorax*. 2000;55(6):449-453.
38. Liu MC, Hubbard WC, Proud D, et al. Immediate and late inflammatory responses to ragweed antigen challenge of the peripheral airways in allergic asthmatics: cellular, mediator, and permeability changes. *American Review of Respiratory Disease*. 1991;144(1):51-58.
39. Costa-Pinto FA, Basso AS, Russo M. Role of mast cell degranulation in the neural correlates of the immediate allergic reaction in a murine model of asthma. *Brain, behavior, and immunity*. 2007;21(6):783-790.
40. Nyenhuis S, Schwantes E, Mathur S. Neutrophil Inflammatory Mediators in Older Asthma Subjects. *Journal of allergy and clinical immunology*. 2010;125(2):AB46.
41. Fehrenbach H, Wagner C, Wegmann M. Airway remodeling in asthma: what really matters. *Cell and tissue research*. 2017;367(3):551-569.
42. Groneberg D, Quarcoo D, Frossard N, et al. Neurogenic mechanisms in bronchial inflammatory diseases. *Allergy*. 2004;59(11):1139-1152.
43. National AE, Prevention P. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. *The Journal of allergy and clinical immunology*. 2007;120(5 Suppl):S94.
44. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *European Respiratory Journal*. 2005;26(2):319-338.
45. Bernstein IL, Li JT, Bernstein DI, et al. Allergy diagnostic testing: an updated practice parameter. *Annals of allergy, asthma & immunology*. 2008;100(3):S1-S148.
46. Korevaar DA, Westerhof GA, Wang J, et al. Diagnostic accuracy of minimally invasive markers for detection of airway eosinophilia in asthma: a systematic review and meta-analysis. *The Lancet Respiratory Medicine*. 2015;3(4):290-300.
47. Boulet L-P, Boulay M-È, Chanez, et al. Asthma-related comorbidities. *Expert review of respiratory medicine*. 2011;5(3):377-393.
48. European Community Respiratory Health Survey Questionnaires Available: <http://www.ecrhs.org/quests.htm>. Accessed December 11, 2015.
49. Asher M, Anderson H, Stewart A, et al. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *European Respiratory Journal*. 1998;12(2):315-335.
50. Sá-Sousa A, Jacinto T, Azevedo LF, et al. Operational definitions of asthma in recent epidemiological studies are inconsistent. *Clinical and translational allergy*. 2014;4(1):24.
51. Daines L, McLean S, Buelo A, et al. Systematic review of clinical prediction models to support the diagnosis of asthma in primary care. *NPJ primary care respiratory medicine*. 2019;29(1):19.
52. Pekkanen J, Sunyer J, Anto J, et al. Operational definitions of asthma in studies on its aetiology. *European Respiratory Journal*. 2005;26(1):28-35.

53. Kirenga BJ, Schwartz JI, de Jong C, et al. Guidance on the diagnosis and management of asthma among adults in resource limited settings. *African health sciences*. 2015;15(4):1189-1199.
54. Uganda population 2019 Available: <http://worldpopulationreview.com/countries/uganda-population/>. Accessed March 14, 2019.
55. Uganda country profile Available: <https://www.bbc.com/news/world-africa-14107906>. Accessed March 14, 2019.
56. UNdata | country profile | Uganda Available: http://data.un.org/CountryProfile.aspx/_Images/CountryProfile.aspx?crName=Uganda. Accessed March 14, 2019.
57. United Nations, Department of Economic and Social Affairs, Population Division (2017). World Population Prospects: The 2017 Revision, custom data acquired via website. Available: <https://population.un.org/wpp/DataQuery/>. Accessed March 14, 2019.
58. National Population and Housing Census 2014- Main Report Available: https://www.ubos.org/wp-content/uploads/publications/03_20182014_National_Census_Main_Report.pdf. Accessed March 14, 2019.
59. World Health Organisation- Countries- Uganda Available: <https://www.who.int/countries/uga/en/>. Accessed March 14, 2019.
60. HEALTH SECTOR DEVELOPMENT PLAN 2015/16 - 2019/20 Available: http://health.go.ug/sites/default/files/Health%20Sector%20Development%20Plan%202015-16_2019-20.pdf. Accessed March 14, 2019.

CHAPTER 2: Prevalence and factors associated with asthma among adolescents and adults in Uganda: a general population-based survey

Authors

Bruce J Kirenga¹, Corina de Jong², Wincelous Katagira³, Samuel Kasozi³, Levicatus Mugenyi^{3,4}, Marike Boezen⁵, Thys van der Molen² and Moses R Kamya⁶

1. Makerere University Lung Institute & Pulmonology Unit, Department of Medicine, Makerere University College of Health Sciences, Kampala, Uganda; Email: brucekirenga@yahoo.co.uk
2. GRIAC-Primary Care, department of General Practice and Elderly Care, University of Groningen, University Medical Center Groningen (UMCG), The Netherlands; Groningen Research Institute for Asthma and FIXED AIRFLOW OBSTRUCTION (GRIAC), University of Groningen, University Medical Center Groningen (UMCG), The Netherlands; Email: c.de.jong02@umcg.nl
3. Makerere University Lung Institute, Makerere University College of Health Sciences, Kampala, Uganda; Email: wincegira@gmail.com
4. Center for Statistics, Interuniversity Institute for Biostatistics and statistical Bioinformatics, UHasselt (Hasselt University), Diepenbeek, Belgium; Email: lmugenyi005@gmail.com
5. Department of Epidemiology, University of Groningen, Groningen, The Netherlands, h.m.boezen@umcg.nl
6. Moses R Kamya, Department of Medicine, Makerere University College of Health Sciences, Kampala, Uganda; Email: mkamaya@infocom.co.ug

Published in BMC public health. 2019 Dec;19(1):227.

ABSTRACT

Background: Recent large-scale population data on the prevalence of asthma and its risk factors are lacking in Uganda. This survey was conducted to address this data gap.

Methods: A general population-based survey was conducted among people ≥ 12 years. A questionnaire was used to collect participants socio-demographics, respiratory symptoms, medical history, and known asthma risk factors. Participants who reported wheeze in the past 12 months, a physician diagnosis of asthma or current use of asthma medications were classified as having asthma. Asthmatics who were ≥ 35 years underwent spirometry to determine how many had fixed airflow obstruction (i.e. post bronchodilator forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio < lower limit of normal (LLN). Descriptive statistics were used to summarize participants' characteristics. Prevalence of asthma was calculated as a proportion of asthmatics over total survey population. To obtain factors independently associated with asthma, a random-effects model was fitted to the data.

Results: Of the 3,416 participants surveyed, 61.2% (2088) were female, median age was 30 years (IQR, 20-45) and 323 were found to have asthma. Sixteen people with asthma ≥ 35 years had fixed airflow obstruction. The prevalence of asthma was 11.0% (95% CI: 8.9 – 13.2; males 10.3%, females 11.4 %, urban 13.0% and rural 8.9%. Significantly more people with asthma smoked than non-asthmatics: 14.2% vs. 6.3%, $p < 0.001$, were exposed to biomass smoke: 28.0% vs. 20.0%, $p < 0.001$, had family history of asthma: 26.9% vs. 9.4%, $p < 0.001$, had history of TB: 3.1% vs. 1.30%, $p = 0.01$, and had hypertension: 17.9% vs. 12.0%, $p = 0.003$. In multivariate analysis smoking, (adjusted odds ratio (AOR), 3.26 (1.96 – 5.41, $p < 0.001$) family history of asthma, AOR 2.90 (98 – 4.22 $p < 0.001$), nasal congestion, AOR 3.56 (2.51 – 5.06, $p < 0.001$), biomass smoke exposure, AOR 2.04 (1.29 – 3.21, $p = 0.002$) and urban residence, AOR 2.01 (1.23 – 3.27, $p = 0.005$) were independently associated with asthma.

Conclusion: Asthma is common in Uganda and is associated with smoking, biomass smoke exposure, urbanization, and allergic diseases. Health care systems should be strengthened to provide asthma care. Measures to reduce exposure to the identified associated factors are needed.

Key words: Asthma, prevalence, Uganda

2.1 BACKGROUND

Asthma is estimated to affect 334 million people globally.¹ Recent large-scale population data on the prevalence of asthma and its risk factors are lacking in Uganda in particular and Africa in general. The world health survey conducted between 2002-2003 reported an asthma prevalence of 4-8% in the studied African countries.¹ A systematic review by Adeboye et al found that the weighted mean prevalence of asthma was 7.0% in the rural areas (2.5-11.5) and 9.6% (3.9-15.2) in urban areas.² The same systematic review also indicates that the number of people suffering from asthma in Africa has increased from 74.4 million in 1990 to 119.3 million in 2010.

In addition to genetic susceptibility, several factors have been found to be associated with asthma.³ These factors include exposure to allergens such as pollen and house dust mites, indoor air pollution (biomass smoke) and outdoor air pollution, tobacco smoking including second hand smoke (especially in children), urban residence and viral respiratory infections.^{3-6, 7}

Diagnosing asthma is challenging as there is no gold standard test. A combination of characteristic clinical features and various tests (spirometry, airway inflammation, bronchial hyper-responsiveness testing, allergy testing) is used to arrive at a diagnosis in a clinical setting.⁸ In surveys however, extensive clinical evaluation and testing is often not possible, hence surveys have relied mainly on symptom questionnaires. The three most commonly used questionnaires are those used in international study of asthma and allergy in childhood (ISAAC), the European community respiratory health survey (ECRHS) and the world health survey questionnaires.^{1, 9, 10}

To fill the data gap on asthma prevalence and its risk factors in Uganda, we aimed to conduct a national general population-based survey.

2.2 METHODS

Design and study participants

This study was a cross-sectional general population-based survey in five districts in Uganda: Kampala (urban) and Iganga, Kiruhura, Maracha and Pader (rural), Figure 1. The overall calculated sample size was 2936 participants (518 from each of 4 rural districts and 864 from Kampala) based on the assumption of an asthma prevalence of 8%, a precision of 0.03 and a design effect of 1.5 (to account for the cluster design). Clusters (villages) were selected by probability proportionate to size by Uganda Bureau of Statistics using the Uganda National population and housing census of 2014. Households within clusters were selected by simple random sampling from a household list generated by village leaders. All persons aged ≥ 12 who were members of selected household and provided written informed consent (and assent in case of minors) were surveyed. Exclusion criteria were: residency of congregation settings (schools, prisons, homes) and temporary residents (less than 2 weeks in household of selected villages). According to the Uganda National population and housing census of 2014, the average number of persons 12 years and older in a household was estimated to be 2.5 persons and the average number of households per cluster was 90 households. Based on these estimates we surveyed a total of 1408 households in 60 clusters across the country; 20 clusters in Kampala and 20 households from each of the clusters and in rural districts we surveyed 10 clusters and 25 households from each of the districts.

Figure 1. Survey districts (highlighted in blue), based on UN map of Uganda- including new districts by region

Survey implementation

In this survey three field teams each comprising of one supervisor, two interviewers, one spirometry technician, one district tuberculosis and leprosy supervisor (DTLS), one local council 1 leader (LC1), one driver and community volunteers as needed was used. Each team surveyed one cluster per day (i.e. about 50 participants/day). The implementation of the survey commenced with the training of the survey teams. Thereafter, a pilot was undertaken to test survey human resources, study tools and the designed data system. After the pilot, adjustments to the tools and the data management system were made. The teams were retrained. Halfway into the survey, amid term review was conducted to inform the investigators of any needed adjustments and strategies to enhance the survey quality.

Survey procedures

Sampled participants were interviewed by trained research assistants using a standardized questionnaire developed by adapting questions from internationally recognized questionnaires, namely the World Health Organization (WHO) health survey^{1, 10}, the ISAAC¹⁰ and ECRHS surveys⁹. Participants who reported either wheeze in the last 12 months, history of current use of asthma medications at the time of the survey or history of ever having a physician diagnosis of asthma were considered to be asthmatics.

Anthropometric measurements were measured; height (measured without shoes to the nearest 0.1-centimeter using a stadiometer [SECA; Hamburg, Germany]) and weight (measured without shoes and in light clothing to the nearest 0.1 kilogram using a calibrated beam scale). Blood pressure (BP) was measured using an Omron automated sphygmomanometer model HEM-907, which has an adjustable cuff size. Participants assumed a resting seated posture ≥ 10 minutes prior to two sequential BP readings taken 10 minutes apart. We considered the average of the two BP readings as the individual's BP. Participants with systolic BP >130 and diastolic BP >90 were considered to have hypertension for purposes of this analysis.

Participants who fulfilled the criteria for asthma on questionnaire and were ≥ 35 years underwent spirometry testing to assess for presence of fixed airflow obstruction. The 35 year cut off limit was chosen because fixed air flow obstruction increases with age and based on our previous surveys we found many persons with fixed airflow obstruction from age 35 years and older.¹¹ Participants identified as having asthma were referred to nearest health facilities for further evaluation and management. Spirometry was conducted and interpreted according to American Thoracic Society/European Respiratory Society guidelines using a Pneumotrac[®] spirometer with Spirotrac[®] V software (Vitalograph Ltd., Buckingham, United Kingdom).¹² Spirometry was performed with participant seated and with a nose clip applied. Testing continued until at least three acceptable and reproducible blows with the largest and second-largest values for both forced vital capacity (FVC) and forced expiratory volume in 1s (FEV₁) within 150 mL or no more than 5% difference; the largest values for FVC and FEV₁ were considered the best and used for analysis. Spirometers were calibrated every morning with a 3 L syringe. Pre-bronchodilator spirometry was performed. Participants whose FEV₁/FVC ratio was less than 80% underwent post bronchodilator spirometry (i.e. repeat spirometry 15 minutes after inhalation of 400 micrograms of inhaled salbutamol). On a daily basis, a physician reviewed all spirograms and those that did not meet the quality criteria were repeated the following day. Predicted parameters were based on NHANES III models as in built within the Spirotrac[®] V spirometers program used.¹³ Participants whose post bronchodilator FEV₁/FVC ratio was less than the LLN ie, participants below the fifth percentile of the predicted FEV₁/FVC ratio (calculated with GLI2012 Data Conversion software; version 3.3.1) were classified as having fixed airflow obstruction.^{14, 15} However these participants were not excluded from asthma participants on this basis.

Ethical approval

Ethics approval was obtained from the Mulago Hospital Research and Ethics committee and the Uganda National Council for Science and Technology. Participants provided written informed consent and were free to terminate study participation at any time during the study. For children between the ages of 12-18 years we obtained their written assent and written parental/legal guardian consent.

Statistical analysis

The planned sample size was 2936 participants, sufficient to provide a precise national, rural vs. urban and male vs. female estimates assuming a national asthma prevalence of 8%. Urban setting was defined as any areas gazette by the government of Uganda as urban during the 2014 national housing and population census.¹⁶

Prevalence of asthma was calculated as the proportion of participants with asthma in the survey population and presented with 95% confidence intervals (95% CI). Weighting to account for clustering due to the cluster design of the survey was performed. A weight, which is the reciprocal of the overall selection probability (p) was generated as $1/p$ where $p=p_1*p_2*p_3$ with p_1 , p_2 and p_3 being the probabilities of selecting a district, a cluster within a district, and a household within a cluster, respectively. Later, “svy:” command in Stata was used to apply the weights when estimating the prevalence and other statistics. Because weighted and unweighted prevalence estimates differed, we present the weighted prevalence estimates in this manuscript. Descriptive statistics was used to summarize participants’ characteristics.

To obtain factors independently associated with asthma, a random-effects model was fitted to the data.¹⁷ All factors that were individually associated with asthma with $p\text{-value}<0.20$ and demographic factors were subjected to multivariable analysis using a random-effects model. To arrive at a better fit, backward model building was conducted using likelihood ratio test (LRT), the multicollinearity was checked using the variance inflation factor (VIF). The results from a better fit and free from multicollinearity ($VIF<10$) are presented as adjusted estimates. Data was analyzed using STATA (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

2.3 RESULTS

Characteristics of study participants

From September 15th to October 10th, 2016, 4310 participants were invited and 3416 participated (participation rate of 79.3%). Of 3416 participants, 61.2% (2088) were female, 22.78% (778) were of urban residence and the median age was 30 years (IQR 20-45). Further details of participants’ characteristics are shown in Table 1.

Table 1. Characteristics of study participants (social, demographic, risk factors, respiratory and allergy symptoms, and comorbidities)-Percent distribution by asthma status

Characteristic	Number	Percentage
Residence		
Urban	779	22.80
Rural	2637	77.20
Gender		
Male	1327	38.85
Female	2089	61.15
Age in years		
<15	372	10.89
15-24	883	25.86
25-34	681	19.94
35-44	577	16.90
45-54	475	13.91
55-64	225	5.92
65+	202	
Allergy symptoms		
Nasal congestion in the past 12 months	538	15.75
Itchy-watery eyes in the past 12 months	767	22.45
Skin rash in the past 12 months	408	11.96
Rash affected other areas	261	62.74
Respiratory symptoms		
Cough	711	20.83
Shortness of breath	309	9.05
Chest pain	873	25.56
Sputum production	257	7.52
Risk factors		
History of /passive smoking	242	7.09
Exposure to bio-mass†	698	20.44
Family history of asthma‡	377	11.05
History of TB treatment	50	1.45
HIV positive	103	3.02
Hypertensive	426	12.58

†Including use of wood, charcoal and kerosene for cooking or lighting

‡History of wheezing or asthma by participant's mother and/or any family member

Prevalence of asthma

Overall 323 participants were found to have asthma. Three hundred and eighteen of 323 asthmatic participants (9.3%), 58/323 (1.7%), and 25/323 (0.7%) reported to have had wheezing the past 12 months, had ever had physician's diagnosis of asthma, and were currently using asthma medications at the time of the survey, respectively. A Venn diagram showing overlaps between these three measures of asthma is presented in Figure 2. The weighted prevalence of asthma was 11.02% (95% CI: 8.87 – 13.17), males 10.27% (95% CI: 7.88 – 12.65), females 11.40 % (95% CI: 8.71 – 14.09), urban 12.99% (95% CI: 9.03 – 16.95), rural 8.86% (95% CI: 7.74 – 9.98), Table 2. Among both males and females, the asthma prevalence increased with increasing age, Figure 3

Fig. 2. A Venn-diagram showing asthma prevalence by three diagnostic criteria and overlap between them

Table 2. Prevalence of asthma (**Overall**, by residence, gender, and age group)

	Unweighted number n/N	Weighted prevalence	
		%	95% CI
Overall	323/3416	11.02	8.87 – 13.17
Residence			
Rural	227/2637	8.86	7.74 – 9.98
Urban	96/779	12.99	9.03 – 16.95
Gender			
Male	114/1327	10.27	7.88 – 12.65
Female	209/2089	11.40	8.71 – 14.09
Age group			
<15	19/372	7.99	1.89 – 14.09
15-24	54/883	8.68	5.44 – 11.93
25-34	65/681	10.56	6.75 – 14.37
35-44	66/577	14.42	9.99 – 18.85
45-54	53/475	11.81	8.09 – 15.53
55-64	31/225	14.37	7.17 – 21.57
65+	35/201	13.66	8.06 – 19.25

Figure 3. Prevalence of asthma by age group and gender

Comparison of characteristics of asthmatic and non-asthmatic survey participants

More asthmatics than non-asthmatics reported tobacco smoke exposure 14.2% vs. 6.3%, $p < 0.001$, biomass smoke exposure 28.0% vs. 19.7%, $p < 0.001$, family history of asthma 26.9% vs. 9.4%, $p < 0.001$, history of tuberculosis (TB) 3.1% vs. 1.3%, $p = 0.010$, and hypertension 17.9% vs. 12.0%, $p = 0.003$, supplementary Table 1

The proportions of participants with allergy and respiratory symptoms by asthma status are presented in supplementary Table 2A & 2B. Nasal congestion in the past 12 months was reported by 40.3% of asthmatics vs. 13.2% non-asthmatics, $p < 0.001$. Itchy watery eyes were reported by 40.6% of asthmatics vs. 20.6% non-asthmatics, $p < 0.001$ while skin rash was reported by 20.7% of asthmatics vs. 11.0% non-asthmatics, $p < 0.001$. The proportions of the different respiratory symptoms by asthma vs. non-asthma status respectively were: cough (51.7% vs. 17.6%, $p < 0.001$), shortness of breath (40.3% vs. 5.8%, $p < 0.001$), chest pain (56.7% vs. 22.3%, $p < 0.001$) and sputum production (28.5% vs. 5.3%, $p < 0.001$).

Factors associated with asthma

The factors independently associated with asthma in this survey as obtained from an adjusted random-effects model were: smoking, adjusted odds ratio (AOR) 3.26 (95% CI: 1.96 – 5.41, $p < 0.001$), family history of asthma, AOR 2.90 (95% CI: 1.98 – 4.22, $p < 0.001$), nasal congestion in the past 12 months, AOR 3.56 (95% CI: 2.51 – 5.06, $p < 0.001$), biomass smoke exposure, AOR 2.04 (95% CI: 1.29 – 3.21, $p = 0.02$) and urban residence, AOR 2.01 (95% CI: 1.23 – 3.27, $p = 0.05$), Table 3. All respiratory symptoms were associated with asthma, AORs (95% CIs) of: cough 2.41 (1.66-3.50, $p < 0.001$), shortness of breath 6.84 (4.57-10.23, $p < 0.001$), chest pain 3.00 (2.15-4.19, $p < 0.001$) and sputum production 1.81 (1.16-2.88, $p = 0.009$), Table 3. The factors associated with asthma in a model that considers only factors associated with asthma with a p-value less 0.05 at a bivariate stage are shown in supplementary Table 3.

Table 3. Factors associated with asthma.

Factors	With asthma n (%)	Without Asthma n (%)	Crude estimates		Adjusted estimates	
			Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
History of /passive smoking						
Yes	46 (14.24)	196 (6.34)	2.80 (1.89 – 4.14)	<0.001	3.26 (1.96 – 5.41)	<0.001
No	277 (85.76)	2896 (93.66)	1		1	
Family history of asthma [‡]						
Yes	87 (26.93)	290 (9.39)	3.57 (2.68 – 4.76)	<0.001	2.90 (1.98 – 4.22)	<0.001
No	236 (73.07)	2800 (90.61)	1		1	
Nasal congestion in the past 12 months						
Yes	130 (40.25)	408 (13.20)	5.06 (3.79 – 6.75)	<0.001	3.56 (2.51 – 5.06)	<0.001
No	193 (59.75)	2684 (86.80)	1		1	
Cough						
Yes	167 (51.70)	544 (17.60)	6.48 (4.76 – 8.82)	<0.001	2.41 (1.66 – 3.50)	<0.001
No	156 (48.30)	2547 (82.40)	1		1	
Shortness of breath						
Yes	130 (40.25)	179 (5.79)	14.24 (9.90 – 20.50)		6.84 (4.57 – 10.23)	<0.001
No	193 (59.75)	2911 (94.21)	1		1	
Chest pain						
Yes	183 (56.66)	690 (22.32)	5.35 (4.04 – 7.08)	<0.001	3.00 (2.15 – 4.19)	<0.001
No	140 (43.34)	2402 (77.68)	1		1	
Sputum production						
Yes	92 (28.48)	165 (5.33)	9.01 (6.22 – 13.07)	<0.001	1.83 (1.16 – 2.89)	0.009
No	231 (71.52)	2928 (94.67)	1		1	
Exposure to bio-mass [†]						
Yes	90 (27.95)	608 (19.66)	1.60 (1.20 – 2.14)	0.001	2.04 (1.29 – 3.21)	0.002
No	232 (72.05)	2485 (80.34)	1		1	
Residence						
Urban	96 (29.72)	683 (22.08)	1.48 (1.11 – 1.97)	0.007	2.01 (1.23 – 3.27)	0.005
Rural	227 (70.28)	2410 (77.92)			1	
Sex:						
Female	209 (64.71)	1880 (60.78)	1.17 (0.91 – 1.50)	0.227	1.25 (0.89 – 1.74)	0.195
Male	114 (35.29)	1213 (39.22)	1		1	

[‡]History of wheezing or asthma by participant's mother and/or any family member

[†]Including use of wood, charcoal and kerosene for cooking or lighting

Fixed airflow obstruction

Of the 323 participants who were classified as having asthma on the questionnaire, 138 (42.72%) were 35 years and older and therefore eligible for spirometry. Of these, 120 (86.96%) underwent spirometry and 18(13.04%) did not. We obtained interpretable spirometry in 106 of the 120 (88.33%). After post bronchodilator testing, 16 of the 106 participants who underwent spirometry were confirmed to have fixed airflow obstruction (15.09%), 13(12.26%) had significantly reversible airflow obstruction (i.e. FEV₁ reversibility of >12% or >200mls) and 9 (8.49%) had a restriction.

2.4 DISCUSSION

This survey found an asthma prevalence of 11.02% in Uganda, higher in urban areas than rural areas (12.99% vs. 8.86%) and among those aged 35-44 years (14.42%) compared to those either younger or older than those in this age group. No significant differences were found by gender (female 11.40% and male 10.27%). Significant associations were found between asthma and smoking, family history of asthma, nasal congestion, biomass smoke exposure, urban residence, and all respiratory symptoms. Asthmatic and non-asthmatic participants had statistically significant differences in the rates of history of TB (3.10% vs. 1.30% and hypertension (17.87% vs. 12.03%).

The prevalence of asthma and its higher rate in urban areas found in this survey are comparable to the prevalence reported in previous asthma surveys in Africa.^{2, 1, 2, 18, 19} There are no prior asthma surveys in Uganda among adolescents and adults apart from one report of history of asthma in pregnant women (6.0% was reported)²⁰ Although the sex differences in asthma prevalence were small, the difference was bigger among rural participants (female 9.35% vs. 8.16% for males) than urban participants (females 13.22% vs. males 12.91%). The bigger difference in rural areas could be due to biomass smoke exposure, which is greater in females. Biomass smoke exposure has been found to be associated with asthma in this study and several previous studies.^{19, 21} The smaller difference in urban areas could be attributed to higher ambient air pollution. We have previously shown that air quality in Kampala, where the urban sample was drawn, exceeds safety limits by 5 times.²²

Analysis of the relation between age and asthma shows that asthma peaked in the 35-44 age groups with another peak in those >55 years. The peak in the 35-44 age group is previously reported.²³ The second peak of asthma that we observed in this study could be due to chronic obstructive pulmonary disease (COPD) that increases in prevalence with increasing age²⁴ and given the fact that we defined asthma by symptoms such as wheeze which can overlap with those of COPD. It is therefore possible that some of the patients that we counted as asthma could have had COPD. The prevalence of COPD has been found to be as high as 16% in some places in Uganda.¹¹ To address the issue of older asthmatics having COPD we analyzed the data taking all those who had fixed airflow obstruction as COPD and found that only 5% of all asthmatic could be reclassified as COPD. Our results therefore support other studies' findings that asthma is an important respiratory disease in older people.²⁵ It must be noted however that fixed airflow obstruction can occur in asthmatics even in the absence of COPD due to airway remodeling with long standing asthma especially if care is suboptimal. There are several risk factors for this occurrence namely severe asthma, long-standing and poorly treated or untreated disease, late onset asthma, smoking, frequent exacerbations, ongoing exposures to asthma triggers, persistent eosinophilic airway inflammation and asthma-COPD overlap.^{19, 26-29} In this survey 98.5% of the asthmatics were neither diagnosed nor on asthma treatment that could have led to fixed airflow obstruction.

This survey confirmed the association of several known risk factors with asthma namely smoking, biomass exposure, allergy, respiratory symptoms, and urban residence. We were also able to show a significant association between biomass smoke exposure and asthma. The rates of TB and hypertension were statistically significantly higher among asthmatics in comparison to non-asthmatics: TB (3.10% vs. 1.30%, $p=0.010$) and hypertension (17.87% vs. 12.03%, $p=0.003$). TB has been reported to be associated with asthma in previous studies including a large South Africa population based study.^{19, 30} although the data is limited, the association between hypertension and asthma has also been previously reported.³¹⁻³³

This survey had limitations of geographical coverage (only 5 districts included), not including questions to assess occupational asthma and being conducted in the wet season without comparison with the dry season. Although we had large numbers of males and females the overall proportion of males was lower in the sample. We adjusted for this difference in all analyses but this could have introduced a bias in the sex differences in the prevalence. Although, cross-sectional data cannot be used to draw conclusions on causality, the identified risk factors are well in line with previous prospective studies in other populations.

2.5 Conclusion

Asthma is common in Uganda and is associated with smoking, biomass smoke exposure, urbanization, and allergic diseases. Health care systems should be strengthened to provide asthma care. Measures to reduce exposure to the identified associated factors are needed.

List of abbreviations

AOR	Adjusted odds ratio
ATS	American Thoracic Society
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
ECRHS	European community respiratory health survey
ERS	European Respiratory Society
FVC	Forced vital capacity
FEV ₁	Forced expiratory volume in the first second
IQR	Interquartile range
ISAAC	International study of asthma and allergies in childhood
LRT	Likelihood ratio test
NHANES	National health and nutrition examination survey
TB	Tuberculosis
VIF	Variance inflation factor
WHO	World Health Organization

Declarations

Ethics approval and consent to participate: Ethics approval was obtained from the Mulago Hospital Research and Ethics committee and the Uganda National Council for Science and Technology. Participants provided written informed consent and were free to terminate study participation at any time during the study. For children between the ages of 12-18 years we obtained their assent and parental/legal guardian consent.

Consent for publication

Not applicable, this manuscript does not contain any personal data.

Availability of data and material: The data of the Uganda National Survey is available with the authors.

Competing interests: All authors declare no conflict of interest relevant to this manuscript

Funding: NIH (Award No. R24 TW008861) and NCS, UMCG, The Netherlands. The funders had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Authors' contributions: BK, TvdM, MK, MB and CdJ conceived and designed the survey, supervised data collection and interpreted the data. BK and LM analyzed the data. BK, SK and WK participated in and supervised data collection. All authors read and approved.

Acknowledgements: The authors thank all study participants and research assistants as well as research managers who were involved in this study. Special thanks go to the data management team that ensured that all data was entered and available for analysis in a timely manner.

Authors' Information

Not applicable. No relevant author details available

REFERENCES

1. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC public health*. 2012;12(1):204.
2. Adeboye D, Chan KY, Rudan I, Campbell H. An estimate of asthma prevalence in Africa: a systematic analysis. *Croatian medical journal*. 2013;54(6):519-31.
3. Castro-Rodriguez JA, Forno E, Rodriguez-Martinez CE, Celedón JC. Risk and protective factors for childhood asthma: what is the evidence? *The Journal of Allergy and Clinical Immunology: In Practice*. 2016;4(6):1111-22.
4. Cazzoletti L, Marcon A, Corsico A, Janson C, Jarvis D, Pin I, et al. Asthma severity according to Global Initiative for Asthma and its determinants: an international study. *International archives of allergy and immunology*. 2010;151(1):70-9.
5. Wong K, Rowe B, Douwes J, Senthilselvan A. International prevalence of asthma and wheeze in adults: Results from the world health survey. *B47 ASTHMA EPIDEMIOLOGY: CLINICAL AND PHARMACOLOGICAL DETERMINANTS OF ASTHMA OUTCOMES: Am Thoracic Soc*; 2010. p. A3117-A.
6. Beasley R, Crane J, Lai CK, Pearce N. Prevalence and etiology of asthma. *Journal of allergy and clinical immunology*. 2000;105(2):S466-S72.
7. Okada H, Kuhn C, Feillet H, Bach JF. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. *Clinical & Experimental Immunology*. 2010;160(1):1-9.
8. Global Strategy for Asthma Management and Prevention (2016 update). [cited 2017 April 18]; Available from: ginasthma.org/wp-content/uploads/2016/04/GINA-2016-main-report_tracked.pdf
9. European Community Respiratory Health Survey Questionnaires. [cited 2015 December 11]; Available from: <http://www.ecrhs.org/quests.htm>.
10. Asher M, Anderson H, Stewart A, Crane J, Ait-Khaled N, Anabwani G, et al. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *European Respiratory Journal*. 1998;12(2):315-35.
11. van Gemert F, Kirenga B, Chavannes N, Kamya M, Luzige S, Musinguzi P, et al. Prevalence of chronic obstructive pulmonary disease and associated risk factors in Uganda (FRESH AIR Uganda): a prospective cross-sectional observational study. *The Lancet Global Health*. 2015;3(1):e44-e51.
12. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *European Respiratory Journal*. 2005;26(2):319-38.
13. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *American journal of respiratory and critical care medicine*. 1999;159(1):179-87.
14. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *European Respiratory Journal*. 2012;40(6):1324-43.
15. Sá-Sousa A, Jacinto T, Azevedo LF, Morais-Almeida M, Robalo-Cordeiro C, Bugalho-Almeida A, et al. Operational definitions of asthma in recent epidemiological studies are inconsistent. *Clinical and translational allergy*. 2014;4(1):24.
16. Vos T, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–

- 2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*. 2017;390(10100):1211-59.
17. Molenberghs G, Verbeke, Geert. *Models for Discrete Longitudinal Data*. 1 ed. New York: Springer-Verlag New York; 2005.
 18. Musaffiri S, Joos G, Van Meerbeeck J. Asthma, atopy, and COPD in sub-Saharan countries: the challenges. *African Journal of Respiratory Medicine* Vol. 2011;7(1).
 19. Ehrlich R, White N, Norman R, Laubscher R, Steyn K, Lombard C, et al. Wheeze, asthma diagnosis and medication use: a national adult survey in a developing country. *Thorax*. 2005;60(11):895-901.
 20. Mpairwe H, Muhangi L, Ndibazza J, Tumusiime J, Muwanga M, Rodrigues LC, et al. Skin prick test reactivity to common allergens among women in Entebbe, Uganda. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 2008;102(4):367-73.
 21. Mishra V. Effect of indoor air pollution from biomass combustion on prevalence of asthma in the elderly. *Environmental Health Perspectives*. 2003;111(1):71.
 22. Kirenga BJ, Meng Q, Van Gemert F, Aanyu-Tukamuhebwa H, Chavannes N, Katamba A, et al. The state of ambient air quality in two Ugandan cities: a pilot cross-sectional spatial assessment. *International journal of environmental research and public health*. 2015;12(7):8075-91.
 23. Wu T-J, Wu C-F, Lee YL, Hsiue T-R, Guo YL. Asthma incidence, remission, relapse and persistence: a population-based study in southern Taiwan. *Respiratory research*. 2014;15(1):135.
 24. Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, et al. An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine*. 2010;182(5):693-718.
 25. Yáñez A, Cho S-H, Soriano JB, Rosenwasser LJ, Rodrigo GJ, Rabe KF, et al. Asthma in the elderly: what we know and what we have yet to know. *World Allergy Organization Journal*. 2014;7(1):8.
 26. Kim SR, Rhee YK. Overlap between asthma and COPD: where the two diseases converge. *Allergy, asthma & immunology research*. 2010;2(4):209-14.
 27. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *New England Journal of Medicine*. 2003;349(15):1414-22.
 28. Phelan PD, Robertson CF, Olinsky A. The Melbourne asthma study: 1964-1999. *Journal of allergy and clinical immunology*. 2002;109(2):189-94.
 29. Boulet L-P. Irreversible airway obstruction in asthma. *Current allergy and asthma reports*. 2009;9(2):168-73.
 30. Karahyla JK, Garg K, Garg RK, Kaur N. Tuberculosis and Bronchial Asthma: Not an Uncommon Association. *Chest Journal*. 2010;138(4_MeetingAbstracts):670A-A.
 31. Dogra S, Ardern CI, Baker J. The relationship between age of asthma onset and cardiovascular disease in Canadians. *J Asthma*. 2007;44(10):849-54.
 32. Yun HD, Knoebel E, Fenta Y, Gabriel SE, Leibson CL, Loftus EV, et al. Asthma and Proinflammatory Conditions: A Population-Based Retrospective Matched Cohort Study. *Mayo Clin Proc*. 2012;87(10):953-60.
 33. Ferguson S, Teodorescu MC, Gangnon RE, Peterson AG, Consens FB, Chervin RD, et al. Factors associated with systemic hypertension in asthma. *Lung*. 2014;192(5):675-83.

2.6 ADDITIONAL FILES

File name: Additional file 1

Title of data: Supplementary tables

Description of data: This file contains 4 tables that present additional data obtained in the survey that we consider important to publish. Supplementary table 1 provides data of the comparison of the social, demographic and clinical characteristics of participants with asthma and those without asthma in the survey, supplementary table 2A presents allergy characteristics of the participants by asthma status while supplementary table 2B presents the respiratory symptoms of the participants by asthma status. Supplementary table 3 presents findings of a multivariate model of the factors associated with asthma considering only factors associated with asthma at the bivariate stage with p-value less than 0.05.

2.7 Supplementary tables

Supplementary table 1. Comparison of social, demographic, risk factors, respiratory and allergy symptoms, and comorbidities characteristics of participants with and without asthma

Characteristic	With asthma n (%)	Without asthma n (%)	p-value
Residence			
Urban	96 (29.72)	683 (22.08)	0.002
Rural	227 (70.28)	2410 (77.92)	
Gender			0.169
Male	114 (35.29)	1213 (39.22)	
Female	209 (64.71)	1880 (60.78)	
Age in years			
<15	19 (5.88)	353 (11.42)	<0.001
15-24	54 (16.72)	829 (26.81)	
25-34	65 (20.12)	616 (19.92)	
35-44	66 (20.43)	511 (16.53)	
45-54	53 (16.41)	422 (13.65)	
55-64	31 (9.60)	194 (6.27)	
65+	35 (10.84)	167 (5.40)	
Allergy symptoms			
Nasal congestion in the past 12 months	130 (40.25)	408 (13.20)	<0.001
Itchy-watery eyes in the past 12 months	131 (40.56)	636 (20.56)	<0.001
Skin rash in the past 12 months	67 (20.74)	341 (11.04)	<0.001
Rash affected other areas	46 (65.71)	215 (62.14)	0.573
Respiratory symptoms			
Cough	167 (51.70)	544 (17.60)	<0.001
Shortness of breath	130 (40.25)	179 (5.79)	<0.001
Chest pain	183 (56.66)	690 (22.32)	<0.001
Sputum production	92 (28.48)	165 (5.33)	<0.001
Risk factors			
History of /passive smoking	46 (14.24)	196 (6.34)	<0.001
Exposure to bio-mass†	90 (27.95)	608 (19.66)	<0.001
Family history of asthma‡	87 (26.93)	290 (9.39)	<0.001
History of TB treatment	10 (3.10)	40 (1.30)	0.010
HIV positive	16 (4.95)	87 (2.81)	0.101
Hypertensive	57 (17.87)	369 (12.03)	0.003

†Including use of wood, charcoal and kerosene for cooking or lighting ‡History of wheezing or asthma by participant's mother and/or any family member

Supplementary table 2A. Allergy, Percent distribution of participants by region, gender and asthma status

Allergies		With asthma			Without asthma			P-value
		Weighted percent	Unweighted percent	Unweighted number n/N	Weighted percent	Unweighted percent	Unweighted number n/N	
Allergy								
Urban								
Males								
Nasal congestion in the past 12 months	Yes	52.23	53.85	14/26	18.34	18.23	33/181	<0.001
	No	47.77	46.15	12/26	81.66	81.77	148/181	
Itchy-watery eyes in the past 12 months	Yes	39.10	38.46	10/26	16.27	16.02	29/181	0.006
	No	60.90	61.54	16/26	83.73	83.98	152/181	
Skin rash in the past 12 months	Yes	17.63	19.23	5/26	14.67	12.67	23/181	0.363
	No	82.37	80.77	21/26	85.33	87.33	158/181	
Rash affected other areas	Yes	58.20	60.00	3/5	47.50	50.00	12/24	>0.999
	No	41.80	40.00	2/5	52.50	50.00	12/24	
Females								
Nasal congestion in the past 12 months	Yes	60.80	60.00	42/70	20.94	21.12	106/502	<0.001
	No	39.20	40.00	28/70	79.06	78.88	396/502	
Itchy-watery eyes in the past 12 months	Yes	48.39	47.14	33/70	21.11	21.31	107/502	<0.001
	No	51.61	52.86	37/70	78.89	78.69	395/502	
Skin rash in the past 12 months	Yes	35.81	34.29	24/70	15.40	14.74	74/502	<0.001
	No	64.19	65.71	46/70	84.60	85.26	428/502	
Rash affected other areas	Yes	64.46	64.00	16/25	57.88	58.11	43/74	0.604
	No	35.54	36.00	9/25	42.12	41.89	31/74	
Rural								
Males								
Nasal congestion in the past 12 months	Yes	28.59	29.55	26/88	10.26	11.34	117/1032	<0.001
	No	71.41	70.45	62/88	89.74	88.66	915/1032	
Itchy-watery eyes in the past 12 months	Yes	34.16	35.23	31/88	19.46	20.74	214/1032	0.002
	No	65.84	64.77	57/88	80.54	79.26	818/1032	
Skin rash in the past 12 months	Yes	11.86	14.77	13/88	9.25	10.09	104/1031	0.168
	No	88.14	85.23	75/88	90.75	89.91	927/1031	
Rash affected other areas	Yes	83.42	83.33	10/12	62.65	64.76	68/105	0.332
	No	16.58	16.67	2/12	37.35	35.24	37/105	
Females								
Nasal congestion in the past 12 months	Yes	38.10	34.53	48/139	9.81	11.04	152/1377	<0.001
	No	61.90	65.47	91/139	90.19	88.96	1225/1377	
Itchy-watery eyes in the past 12 months	Yes	42.08	41.01	57/139	19.70	20.75	286/1378	<0.001
	No	57.92	58.99	82/139	80.30	79.25	1092/1378	
Skin rash in the past 12 months	Yes	18.96	17.99	25/139	8.47	10.18	140/1375	0.005
	No	81.04	82.01	114/139	91.53	89.82	1235/1375	
Rash affected other areas	Yes	61.78	60.71	17/28	63.80	64.34	92/143	0.715
	No	38.22	39.29	11/28	36.20	35.66	51/143	

Supplementary table 2B. Respiratory symptoms, Percent distribution of participants by region, gender and asthma status

Respiratory symptoms		With asthma			Without asthma			P-value
		Weighted percent	Unweighted percent	Unweighted number n/N	Weighted percent	Unweighted percent	Unweighted number n/N	
Urban								
Males								
Cough	Yes	39.52	42.31	11/26	11.34	11.11	20/180	<0.001
	No	60.48	57.69	15/26	88.66	88.89	160/180	
Shortness of breath	Yes	30.16	30.77	8/26	5.00	4.44	8/180	<0.001
	No	69.84	69.23	18/26	95.00	95.56	172/180	
Chest pain	Yes	47.35	46.15	12/26	12.62	12.15	22/181	<0.001
	No	52.65	53.85	14/26	87.38	87.85	159/181	
Sputum production	Yes	25.91	26.92	7/26	5.81	5.52	10/181	<0.001
	No	74.09	73.08	19/26	94.19	94.48	171/181	
Wheezing	Yes	48.82	50.00	13/26	0.00	0.00	0/181	<0.001
	No	51.18	50.00	13/26	100	100	181/181	
Hypertensive	Yes	3.20	3.85	1/26	7.20	6.78	12/177	>0.999
	No	96.80	96.15	25/26	92.80	93.22	165/177	
Females								
Cough	Yes	33.93	32.86	23/70	13.92	13.94	70/502	<0.001
	No	66.07	67.14	47/70	86.08	86.06	432/502	
Shortness of breath	Yes	40.87	41.43	29/70	5.71	5.79	29/501	<0.001
	No	59.13	58.57	41/70	94.29	94.21	472/501	
Chest pain	Yes	42.22	41.43	29/70	14.38	13.94	70/502	<0.001
	No	57.78	58.57	41/70	85.62	86.06	432/502	
Sputum production	Yes	16.66	15.71	11/70	5.45	5.18	26/502	0.001
	No	83.34	84.29	59/70	94.55	94.82	476/502	
Wheezing	Yes	49.57	51.43	36/70	0.00	0.00	0/502	<0.001
	No	50.43	48.57	34/70	100	100	502/502	
Hypertensive	Yes	20.74	20.29	14/69	16.53	16.43	81/493	0.423
	No	79.26	79.71	55/69	83.47	83.57	412/493	
Rural								
Males								
Cough	Yes	63.61	67.05	59/88	21.26	19.20	198/1031	<0.001
	No	36.39	32.95	29/88	78.74	80.80	833/1031	
Shortness of breath	Yes	42.85	43.18	38/88	5.72	5.14	53/1031	<0.001
	No	57.15	56.82	50/88	94.28	94.86	978/1031	
Chest pain	Yes	59.46	61.36	54/88	21.86	20.93	216/1032	<0.001
	No	40.54	38.64	34/88	78.14	79.07	816/1032	
Sputum production	Yes	39.32	39.77	35/88	5.25	5.04	52/1032	<0.001
	No	60.68	60.23	53/88	94.75	94.96	980/1032	
Wheezing	Yes	72.39	75.00	66/88	0.00	0.00	0/1032	<0.001
	No	27.61	25.00	22/88	100	100	1032/1032	
Hypertensive	Yes	11.89	12.64	11/87	6.61	7.40	76/1027	0.080
	No	88.11	87.36	76/87	93.39	92.60	951/1027	
Females								
Cough	Yes	53.95	53.24	74/139	19.77	18.58	256/1378	<0.001
	No	46.05	46.76	65/139	80.23	81.42	1122/1378	
Shortness of breath	Yes	39.79	39.57	55/139	6.25	6.46	89/1378	<0.001
	No	60.21	60.43	84/139	93.75	93.54	1289/1378	
Chest pain	Yes	63.73	63.31	88/139	29.02	27.74	382/1377	<0.001
	No	36.27	36.69	51/139	79.98	72.26	995/1377	
Sputum production	Yes	29.35	28.06	39/139	5.79	5.59	77/1378	<0.001
	No	70.65	71.94	100/139	94.21	94.41	1301/1378	
Wheezing	Yes	79.01	79.86	111/139	0.00	0.00	0/1378	<0.001
	No	20.99	20.14	28/139	100	100	1378/1378	
Hypertensive	Yes	23.80	22.63	31/137	14.63	14.60	200/1370	0.013
	No	76.2	77.37	106/137	85.37	85.40	1170/1370	

Supplementary table 3. Factors associated with asthma (based on a multivariate model including only factors associated with asthma with p-value less than 0.05 at univariate analysis)

Factors	With asthma n (%)	Without Asthma n (%)	Crude estimates		Adjusted estimates	
			Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
History of /passive smoking						
Yes	46 (14.24)	196 (6.34)	2.80 (1.89 – 4.14)	<0.001	2.88 (1.78 – 4.67)	<0.001
No	277 (85.76)	2896 (93.66)	1		1	
Family history of asthma [‡]						
Yes	87 (26.93)	290 (9.39)	3.57 (2.68 – 4.76)	<0.001	3.00 (2.05 – 4.40)	<0.001
No	236 (73.07)	2800 (90.61)	1		1	
History of TB treatment						
Yes	10 (3.10)	40 (1.30)	2.59 (1.19 – 5.62)	0.016	0.98 (0.34 – 2.79)	0.970
No	313 (96.90)	3048 (98.70)	1		1	
Nasal congestion in the past 12 months						
Yes	130 (40.25)	408 (13.20)	5.06 (3.79 – 6.75)	<0.001	3.29 (2.27 – 4.76)	<0.001
No	193 (59.75)	2684 (86.80)	1		1	
Itchy-watery eyes in the past 12 months						
Yes	131 (40.56)	636 (20.56)	2.78 (2.15 – 3.61)	<0.001	1.31 (0.93 – 1.84)	0.118
No	192 (59.44)	2457 (79.44)	1		1	
Skin rash in the past 12 months						
Yes	67 (20.74)	341 (11.04)	2.16 (1.57 – 2.96)	<0.001	1.36 (0.90 – 2.06)	0.142
No	256 (79.26)	2748 (88.96)	1		1	
Cough						
Yes	167 (51.70)	544 (17.60)	6.48 (4.76 – 8.82)	<0.001	2.39 (1.64 – 3.48)	<0.001
No	156 (48.30)	2547 (82.40)	1		1	
Shortness of breath						
Yes	130 (40.25)	179 (5.79)	14.24 (9.90 – 20.50)		7.11 (4.71 – 10.74)	<0.001
No	193 (59.75)	2911 (94.21)	1		1	
Chest pain						
Yes	183 (56.66)	690 (22.32)	5.35 (4.04 – 7.08)	<0.001	2.91 (2.08 – 4.07)	<0.001
No	140 (43.34)	2402 (77.68)	1		1	
Sputum production						
Yes	92 (28.48)	165 (5.33)	9.01 (6.22 – 13.07)	<0.001	1.83 (1.15 – 2.91)	0.010
No	231 (71.52)	2928 (94.67)	1		1	
Exposure to bio-mass [‡]						
Yes	90 (27.95)	608 (19.66)	1.60 (1.20 – 2.14)	0.001	1.28 (0.88 – 1.86)	0.203
No	232 (72.05)	2485 (80.34)	1		1	
Residence						
Urban	96 (29.72)	683 (22.08)	1.48 (1.11 – 1.97)	0.007	1.30 (0.84 – 2.00)	0.243
Rural	227 (70.28)	2410 (77.92)			1	

[‡]History of wheezing or asthma by participant's mother and/or any family member

[†]Including use of wood, charcoal and kerosene for cooking or lighting

CHAPTER 3: The proportion of asthma and patterns of asthma medications prescriptions among adult patients in the chest, accident and emergency units of a tertiary health care facility in Uganda

Authors

Bruce J Kirenga¹ and Martin Okot-Nwang¹

1. Division of Pulmonary and Tuberculosis Medicine, Department of Medicine, Mulago National referral and Makerere College of Health Sciences Teaching Hospital

Corresponding author

Bruce J Kirenga

P.O. Box 7072 Kampala

brucekirenga@yahoo.co.uk

+256782404431

Published in **African Health Sciences Vol 12 No 1 March 2012**

ABSTRACT

Background: Asthma is a common chronic disease with high morbidity. In Uganda, the proportion of asthma in health care facilities and the extent to which asthma management guidelines are followed is unknown.

Objectives: To determine the proportion of adult patients diagnosed with asthma and the proportion of asthma patients that receives recommended asthma therapy prescriptions according to Global Initiative for Asthma (GINA) management and prevention guidelines in the chest clinic and accident and Emergency (A&E) departments in Mulago Hospital.

Methods: A retrospective chart review at Mulago Hospital chest clinic and A&E department from January 1st 2009 to December 31st 2009 was performed. Patients diagnosed with asthma were identified and medications prescribed were recorded. Patients were categorized as having received recommended asthma therapy prescriptions (if therapy was compatible GINA guidelines) or not. Proportions of asthmatics in the two departments and those who received recommended asthma therapy were calculated.

Results: One hundred thirty-four (134) of 792 patients in the chest clinic (16.9%) were diagnosed with asthma. At the A&E four hundred and sixteen (416) patients out of 16,800 (2.5%) were diagnosed with asthma. Sixty-nine point seven (69.7%) were female. The median age was 29 years (range, 19-42). Wheezing was the commonest presenting symptom (55%). Recommended asthma therapy prescriptions were 47.4% for chest clinic and 32.2% of the patients at A&E department received asthma therapy prescriptions as recommended for asthma exacerbations management during hospitalization.

Conclusions: Asthma accounts for a significant proportion of outpatients in the chest clinic. Majority of patients do not receive recommended asthma therapy prescriptions

3.1 INTRODUCTION

Asthma is one of the leading chronic diseases in the world with about 300 million people estimated to have the condition¹. Though the mortality from asthma has tremendously reduced in developed countries, the morbidity remains high with an estimated Disability Adjusted Life year lost (DALYS) of 15 million/year and Years of Life lost to disease (YLD) of 2.2% comparable to diabetes, cirrhosis and schizophrenia^{2,3,4,5,6,7}.

Asthma is defined by the global initiative for asthma management and prevention (GINA) as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. These episodes are usually associated with widespread, but variable airflow obstruction within the lung that is often reversible either spontaneously or with treatment. However, the diagnosis of asthma is in most cases a clinical one⁹. Presence of more than one of the symptoms of wheeze, cough, chest tightness and breathlessness with variable airway obstruction is usually sufficient to make a diagnosis of asthma⁹. The specificity of these symptoms and signs is low because they occur in many other conditions⁹.

Asthma medication if used appropriately leads to reduced asthma morbidity and mortality⁴. Most international asthma management guidelines recommend that patients initially diagnosed with asthma receive short acting beta₂ agonist (SABA) preferably by inhalation combined with inhaled steroid⁹. If poor response is noted the patient should be prescribed a long acting beta₂ agonist (LABA) combined with inhaled steroid. Other add-on medications may include leukotriene receptor antagonists, theophyllines or slow release beta₂ agonist tablets⁹. During exacerbations patients should receive systemic steroid, nebulized SABA and oxygen until the patient is stable and then controlled with inhaled beta agonist and steroid⁹.

While data on asthma prevalence in eastern Africa is estimated at 4.4%¹ and most of the asthma medications prescribers do not follow asthma management guidelines in many Low- and Medium-Income Countries (LMIC)¹⁰. No data exists about asthma prevalence and the extent to which asthma management guidelines are followed in Uganda. Surveys to establish the prevalence of asthma in the community and healthcare facilities are therefore urgently needed. The paucity of data on the extent of following asthma management guidelines also necessitates studies on this matter because factors likely to influence following of the guidelines like high cost of asthma medications compared to patient incomes and inadequate asthma management training are present in Uganda.

In this retrospective chart review we sought to estimate the proportion of asthma patients in the Mulago chest clinic and the Accident and emergency (A&E) department and also establish the proportion of asthma patients that are treated according GINA guidelines.

3.2 METHODS

Design and Setting: This study was a retrospective chart review conducted at Mulago national referral and teaching hospital's chest clinic and A&E department. Mulago Hospital is a 1500 bed capacity hospital. It receives referrals from the whole country as well as neighboring countries in East Africa. In addition to the referrals the hospital acts as a primary care facility for Kampala city with a catchment

population of 1,597,900 ¹¹

The chest clinic is a specialist outpatient clinic that provides care to patients with respiratory diseases. Majority of patients seen in this clinic are referred from other hospitals or clinics within the hospital.

The A&E department is the portal for all emergencies in the hospital. Majority of these are self-referred patients from the surrounding communities.

Data extraction procedure: At the chest clinic a trained research assistant assisted by the chest clinic records officer reviewed the clinic patient's registration register to identify new patients who had attended the clinic from January 1st 2009 to December 31st 2009. They identified patients with doctor-diagnosed asthma. The charts of these patients were subsequently retrieved and underwent a chart review.

Chart review was undertaken using a pretested data collection tool. Demographic data, date of registration and patients' residence were recorded. We also collected information about the symptoms the patient reported to the physician on their first day of attending the clinic and the medication that the physician prescribed.

At the A&E department we reviewed the medical emergency register for the total number of patients seen in the same period. We then identified patients with doctor-diagnosed asthma. At A&E patients' demographics and medication prescribed is all written in a patients' register book. However, symptoms and address are not recorded in this book. These two variables are not available for the A&E patients.

Data analysis: Data was entered in Epidata version 3.1 and exported to Stata version 11 for analysis. We calculated the proportion of asthmatics in the chest clinic and A&E department for the study period.

The proportion of patients who were registered in the rainy and dry season was calculated in an attempt to establish seasonality in case presentation. Rainy season in this study included the months of March, April, May, June, September, October and November. Dry season included the months of December, January, February, July and August.

Patients' residence was classified as urban if they lived in Kampala and Wakiso Districts and rural if they lived in districts other than these two.

Frequencies of the symptoms of chest pain, wheeze, cough, and shortness of breath as well as medications prescribed were analyzed. Medication prescriptions were categorized as either recommended or not (recommended if compatible with GINA asthma management guidelines and not if not compatible the same guidelines) ⁹. At the chest clinic, patients whose prescription included an inhaled steroid and beta₂ agonist at the chest clinic were presumed to have received recommended therapy and their proportion was determined. We assumed that all patients in the chest clinic did not have acute severe asthma.

In the A&E department recommended therapy was defined as patients whose treatment included nebulized beta₂ agonist, systemic steroid and oxygen. We did not collect data on medications prescribed at discharge.

3.3 RESULTS

Proportion of asthma

Chest clinic: From January 1st 2009 through December 31st 2009 792 new patients were registered at the chest clinic. One hundred and thirty-four (16.9%) of these had doctor-diagnosed of asthma.

A&E department: During the same period four hundred and sixteen patients who attended the A&E department had asthma out of the total department attendance of 16,800 patients (2.5%).

Social Demographics and seasonality

Eighty three percent (83%) of the patients were from the urban areas. Females constituted 69.7% of the patients. The median age was 29 years (range, 19-42). The youngest patient was one year seen at the emergency department and the oldest was 85 years. The distribution of the patients in the different age groups and by month of registration is shown Figure 1 & 2

Figure 1: Distribution of Asthma patients in the different age groups

Figure 2: Monthly asthma patient registration at the chest clinic and emergency department

Over all there was no significant difference in the number of patients registered in the rainy season as compared to the dry season, 48.7% 95% CI 46.9-55.6% for the rainy season vs. 51.3% 95% CI 44.4-

.53.1% for the dry season. We however found that there were significantly more patients presenting in the rainy season at the chest clinic than at the emergency department $p=0.009$

Presenting symptoms

The commonest presenting asthma symptom was wheezing with 55% of the patients reporting this symptom. The rest of the symptoms are shown in Table 1

Table1: Asthma symptoms among asthma patients at the chest clinic

Symptom	No of patients	Percentage
Wheezing	44	55.0
Cough	43	53.8
Shortness of breath	43	53.8
Chest pain	18	22.5

Medication prescription

Sixty-four patients (47.4%) in the chest clinic received GINA asthma management guidelines recommended therapy. At the A&E department 97 (23.2%) were treated according to the GINA guidelines.

More than 50% of the patients at both clinics received antibiotics, 70/134 (51.6%) and 278/416 (66.8%) for the chest and A&E respectively). The different asthma medications prescribed are shown in Table 2

Table2: Asthma medications prescription at the chest clinic and the A & E departments

Medications	Department	
	Chest clinic, % (N=134)	A & E department, % (N=416)
Oral Salbutamol	52.6	42.9
Oral Prednisolone	64.2	44.4
Oral Aminophylline	15.8	12.9
Intravenous Aminophylline	1.1	72.4
Antibiotics	51.6	66.8
Inhaled beta ₂ agonist	37.9	11.5
Inhaled steroid	24.2	2.4
Nebulised beta ₂ agonist	5.3	20.7
Nebulised Beta ₂ agonist with oxygen	0	2.4

3.4 DISCUSSION

In Mulago hospital we have found the proportion of doctor- diagnosed asthma to be 16.9% in the chest clinic and 2.5 % in the A&E department. This prevalence is comparable to that found in other tertiary health care facilities in Africa^{14, 15}. We found that 83% of the patients were from Kampala city.

Most of the patients were in the 13-34 age group and up to 70% were female. This is consistent with findings by Gustavo JR and others in an asthma study in Spain and Latin America found that 37.5% of the patients were in the 15-35 age group and 72% were female¹⁹. The commonest asthma symptom was wheezing as has been found in other studies²².

Generally, appropriate asthma treatment was low both at the chest clinic and A&E department but was worse at the emergency department. For example over 50% of the patients received oral salbutamol therapy instead of inhaled salbutamol. The main reason may be cost because inhaled steroid and beta₂ agonist are more expensive than oral steroids and beta₂ agonist. Cost has been recognized as a factor in asthma medication use in many developing countries. Bobby Ramakant wrote in Citizens News Service on 2009 World Health Day that the cost of a combination of inhaler is higher than the monthly salary of a nurse²⁵. In the emergency department only 20.7% of the patients were nebulised and only 2.4% received nebulisation with oxygen despite the fact that nebulisation equipment and oxygen are available in the department most of the time. This finding could be due to lack of awareness on the part of the attending health workers. Studies done in some countries in Africa have shown prescribers do not follow asthma guidelines²⁶. On the other hand in developed countries use of asthma guidelines has improved; by 2006 inhaled steroids use was 89% as compared to 62% in 1995^{27,28}.

The finding of more than half of the patients receiving an antibiotic prescription is more than twice that reported in other studies. In the United States a study found that 22% of the acute asthma was treated with an antibiotic³⁵. Current guidelines do not recommend an antibiotic for asthma unless there is evidence of bacterial infection³⁶. A systematic review evaluating the efficacy of antibiotics in acute asthma failed to show benefit. The high antibiotic prescription in our setting is driven by lack of knowledge concerning asthma management guidelines. Clinicians interpret the cough that the patients present with as being a bacterial infection and therefore prescribe an antibiotic.

We acknowledge that our study has limitations. Firstly, it was a retrospective analysis. We could not find some of the data in the patients file. This mainly affected the symptoms data while all data on medications was available. Secondly, we used doctor diagnosed asthma in this study. It is possible some patients with asthma may have not been given a diagnosis of asthma and vice versa.

Lastly this study was carried out in a tertiary health care facility and therefore these results cannot be representative of what is happening at the population level.

In conclusion this study demonstrates that asthma accounts for a significant proportion of outpatients in the chest clinic. The poor adherence to international asthma management guidelines necessitates urgent need of asthma management training in Mulago Hospital. Local asthma management protocols should be developed and displayed at all points where asthma patients are seen in the hospital. Prospective studies to establish the burden of asthma in the hospital and in the community as well as discharge medications are also needed.

Acknowledgements

We are grateful to all the staff of the Mulago Hospital chest clinic and A&E department. We thank Mulago Hospital Management for allowing us access the records. We acknowledge the contribution of Dr Joseph and Mr. Okot Gabriel for conducting the chart review. Our thanks also go to Mr. Yusufu Mulumba for assisting with the data analysis.

References

1. Masoli M, Fabian D, Holt S, Beasley R. Global Burden of Asthma report, 2004
2. World Health Organization. The global burden of disease: 2004 update, Geneva 2008
3. Jarvis D, Burney P. Epidemiology of asthma. In: Asthma and Rhinitis. Eds: Holgate S, Busse W. Blackwell Scientific Press, Oxford: 1995, 17-32.
4. Murray CJL, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet* 1997; 349: 1436-42.
5. Ait-Khaled N, Enarson D, Bousquet J. Chronic respiratory diseases in developing countries: the burden and strategies for prevention and management. *Bull WHO* 2001; 79:971-9
6. World Health Organization. WHO consultation on the development of a comprehensive approach for the prevention and control of chronic respiratory diseases. Geneva 2001.
7. World Health Organization. Global health risks: mortality and burden of disease attributable to selected major risks, Geneva 2009
8. Mpairwe H, Muhangi L, Ndirizza J, Tumusiime J, Muwanga M, Rodrigues LC et al. Skin prick test reactivity to common allergens among women in Entebbe, Uganda. *Trans R Soc Trop Med Hyg.* 2008; 102(4): 367–373.
9. Global Initiative for Asthma. Global Strategy for asthma management and prevention 2010 (update)
10. Mugusi F, Edwards R, Hayes L, Unwin N, Mbanya JC, Whiting D et al. Prevalence of wheeze and self-reported asthma and asthma care in an urban and rural area of Tanzania and Cameroon. *Trop Doct.* 2004; 34(4):209-14.
11. <http://www.citypopulation.de/Uganda.html>. Retrieved 2011-02-21
12. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variations in the prevalence of asthma symptoms: International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Respir J* 1998; 12: 315±335.
13. Ait-Khaled N, Odhiambo J, Pearce N, Adjoh KS, Maesano IA, Benhabyles B et al. Prevalence of symptoms of asthma, rhinitis and eczema in 13- to 14-year-old children in Africa: the International Study of Asthma and Allergies in Childhood Phase III. *Allergy* 2007;62(3):247-58
14. Wasunna AE. Asthma as seen at the casualty department, Kenyatta National Hospital, Nairobi. *East Afr Med J.* 1968; 45(11):701-5.
15. Desalu OO, Oluwafemi JA, Ojo O. Respiratory diseases morbidity and mortality among adults attending a tertiary hospital in Nigeria. *J Bras Pneumol* 2009; 35(8):745-52.
16. Burney P. The changing prevalence of asthma? *Thorax* 2002; 57(Suppl II): ii36-ii39.
17. Van Niekerk CH, Weinberg EG, Shore SC, De V Heese H, Van Schalkwyk DJ. Prevalence of asthma: a comparative study of urban and rural Xhosa children. *Clinical Allergy* 1979; 9: 319-324.
18. J.A. Odhiambo, L.W. Ng'ang'a, M.W. Mungai, C.M. Gicheha*, J.K. Nyamwaya, F. Karimi et al. Urban–rural differences in questionnaire-derived markers of asthma in Kenyan school children. *Eur Respir J* 1998; 12: 1105–1112
19. Gustavo Javier Rodrigo, Vicente Plaza, Jesús Bellido-Casado, Hugo Neffén, María Teresa Bazús, Gur Levy et al. The study of severe asthma in Latin America and Spain (1994-2004): characteristics of patients hospitalized with acute severe asthma. *J. bras. Pneumol* 2009; 35 (7):635-44

20. European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996; 9: 687-95.
21. Melgert BN, Ray A, Hylkema MN, Timens W, Postma DS. Are there reasons why adult asthma is more common in females? *Curr Allergy Asthma Rep.* 2007; 7:143—50.
22. Becklake MR, Kauffmann F. Gender differences in airway behavior over the human life span. *Thorax* 1999; 54:1119—38.
23. Schatz M, Camargo Jr CA. The relationship of sex to asthma prevalence, health care utilization, and medications in a large managed care organization. *Ann Allergy Asthma Immunol.* 2003; 91:553—5.
24. International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998; 351: 1225-32.
25. Bobby Ramakant. World Asthma Day (5 May 2009) Asthma control is appalling in most countries. Feature Article Citizen News Service (CNS) Sun, 03 May 2009
26. Aït-Khaled N, Enarson DA, Bencharif N, Boulahdib F et al. Implementation of asthma guidelines in health centres of several developing countries. *Int J Tuberc Lung Dis.* 2006;10(1):104
27. Adolf Rodriguez de la Vega, Arnaldo Tejeiro FernLndez. Armando Gómez Echeverria et al. Investigation of the prevalence and inheritance of bronchial asthma in San Antonio De Los Baros, Cuba. *Paho Bulletin.* Vol. ix, no. 3, 1975
28. Salmeron S, Liard R, Elkharrat D, Muir J, Neukirch F, Ellrodt A. Asthma severity and adequacy of management in accident and emergency departments in France: a prospective study. *Lancet* 2001; 358(9282):629-35.
29. Kuo E, Kesten S. A retrospective comparative study of in-hospital management of acute severe asthma: 1984 vs 1989. *Chest* 1993;103(6):1655-61
30. Liou, A et al. Causative and contributive factors to asthma severity and patterns of medication use in patients seeking specialized asthma care. *Chest* 2003; 124:1781-8.
31. Fukutomi Y, Taniguchi M, Tsuburai T, Okada C, Shimoda T, Onaka A et al. Survey of asthma control and anti-asthma medication use among Japanese adult patients. *Arerugi* 2010; 59(1):37-4
32. Alavy B, Chung V, Maggiore D, Shim C, Dhuper S. Emergency department as the main source of asthma care. *J Asthma.* 2006 Sep; 43(7):527-32.
33. [Bouayad Z](#), [Aichane A](#), [Afif A](#), [Benouhoud N](#), [Trombati N](#), [Chan-Yeung M](#) et al Prevalence and trend of self-reported asthma and other allergic disease symptoms in Morocco: ISAAC phase I and III. *Int J Tuberc Lung Dis.* 2006 Apr; 10(4):371-7.
34. Johnston NW, Sears MR. Asthma exacerbations epidemiology. *Thorax.* 2006;61(8):722-8
35. Stefan G. Vanderweil, Chu-Lin Tsai, Andrea J. Pelletier et al. Inappropriate Use of Antibiotics for Acute Asthma in United States Emergency Departments. *Academic Emergency Medicine* 2008; 15:736–743
36. National Heart Lung and Blood Institute. National Asthma Education and Prevention Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda,MD: National Institutes of Health.NIH Publication 08-4051. <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>. Accessed May 20,2008.
37. British Thoracic Society, Scottish Intercollegiate Guidelines network. British Guidelines on Management of Asthma, a national clinical guideline. May 2008(revised June 2009)

CHAPTER 4: Chronic respiratory diseases in a tertiary health care facility in a developing country in Africa: a hospital based descriptive study

Authors

Bruce J Kirenga¹ Lydia Nakiyingi¹ William Worodria¹ Martin Okot-Nwang¹

1. Pulmonology Unit, Department of Medicine, Makerere University/ Mulago Hospital

Corresponding author

Bruce J Kirenga

P.O. Box 7072 Kampala

brucekirenga@yahoo.co.uk

+256782404431

Published in **African Journal of Respiratory Medicine** Vol 8 No 2 March 2013

ABSTRACT

Background: Globally it is being increasingly recognized that non communicable diseases constitute a neglected epidemic especially in low- and middle-income countries. Chronic respiratory diseases are among the most common non communicable diseases but their burden is unknown in many low- and middle-income countries. We conducted a retrospective analysis of data collected on hospitalized patients in a pulmonary ward of Mulago National Referral Hospital between December 2010 and August 2011. The objective of this analysis was to determine the proportion, mortality and average length of stay of patients with chronic respiratory diseases in a tertiary health care facility in Uganda. Demographic characteristics, final diagnosis, vital status at discharge and the average length of stay were extracted from the inpatient database. Proportions of the diagnoses, mortality and average length of stay of the admitted patients calculated.

Results: Five hundred and fifty-eight patients were admitted during the study period, 58.2% were male. The mean age was 37.4 years (17.4 SD). The average length of stay was 5.6 days (8.4SD). Fifty-one patients (9.0%) had chronic respiratory disease. Of these asthma (6.3%) was the most frequent chronic respiratory disease diseases.

Eighty (14.1%) of the admitted patients died during hospitalization; 5 (9.8%) of them were patients with chronic respiratory disease and 73 (14.5%) had communicable disease.

Conclusion: Communicable respiratory diseases still account for the majority of inpatients in Mulago hospital and are associated with high mortality but admission rates and mortality associated with CRD though lower than that of communicable respiratory diseases is higher than in developed settings. There is need for studies that investigate the reasons for admissions and causes of death among patients with CRDs.

4.1 BACKGROUND

Globally non communicable diseases (NCDs) constitute a neglected epidemic especially in low- and middle-income countries. The World Health Organization (WHO) estimates that NCDs account for 63% of all deaths. Further estimates also show that by 2015, 70% of all deaths in people less than 70 years of age will be due to NCDs and that 80% of these deaths will occur in developing countries.¹ The world economic forum estimates that the economic burden of NCDs by 2030 at 47 trillion US dollars but also states that the prevention of these diseases is can cost as low as 0.4 US dollars per person.² Despite the above well-known facts, NCDs do not feature in the millennium development goals and accounted for only 3% of global health aid.³

Efforts are underway to tackle this problem; notable of these is the recently concluded United Nations high level meeting held in September 2011 to rally world leaders to support programs that are aimed at the prevention and care for NCDs. This meeting is the second in the history of the United Nations to be held for a health-related issue after the one on HIV/AIDS in 2001 that lead to the global fund to fight TB, HIV and malaria.⁴

Chronic respiratory diseases (CRD), cardiovascular diseases, cancer and diabetes are the four major NCDs that account for 80% of all NCDs deaths.

CRD refers to chronic diseases of the airways and other structures of the lung. The most common CRDs include asthma and respiratory allergies, chronic obstructive pulmonary disease (COPD), occupational lung disease, pulmonary hypertension and lung cancer. About 300 million people are reported to suffer from asthma, 210 million have COPD and 600 million suffer allergic rhinitis.⁵ The burden of CRDs in Uganda is not accurately known. The WHO estimates that there were 106,400 NCD deaths in Uganda in the year 2010.^{1,6}

Fifty one percent of these were under the age of 60 years (essentially premature preventable deaths)⁶.

From this report CRD were the third leading cause of NCD deaths in Uganda (212.7/100000).⁶

A number of studies to measure the burden of the most important CRDs (asthma and COPD) are underway in different countries in Africa. While it will take time before data from these surveys becomes available, analysis of health care facility data can provide insight into the burden of these diseases.

This study was therefore conducted to estimate the proportion, average length of stay and outcomes of patients admitted with CRD

4.2 METHODS

Design: Retrospective database review

Setting: This study was carried out on data collected on patients admitted on the pulmonary division, Department of Medicine, Mulago National Referral Hospital, Kampala, Uganda. Mulago Hospital is a 1500 bed capacity hospital which doubles as Uganda's national referral hospital as well as a teaching hospital for Makerere University College of health sciences. The hospital receives mainly referred patients from all districts of Uganda but also a big number are self-referred mainly from neighboring districts. The Department of Medicine is organized into 9 specialty units/divisions which include:

Pulmonary Division, Cardiology, Nephrology, Endocrinology, Neurology, Hematology, Rheumatology, Infectious disease and Gastroenterology. Other subspecialty units include: Uganda Cancer Institute, Dermatology clinic Accident and Emergency unit.

The Pulmonary division, with a bed capacity of 50 beds admits patients with respiratory diseases. When admitted, these patients undergo a thorough clinical evaluation and laboratory investigations. The Division also offers services like bronchoscopy and pulmonary function tests. All patients' data is first entered into patient specific files and is later transferred into an electronic database at discharge or death.

Data collection: We extracted data from an electronic patient database for patients whose data was entered from December 2010 to August 2011. Patients admitted to hospital have their demographic data captured on a face sheet of the hospital file. Throughout the course of admission patients are reviewed and all data is recorded in the hospital file. On discharge or death, the final diagnosis and date of discharge is recorded on the patient file face sheet. Hospital records officer classify final diagnosis according to international classification of diseases 10(ICD10). Patient data is then entered into an EPIDATA database.

Patient hospital number, initials, age, sex, date of admission, date of discharge, length of stay, final diagnosis, and outcome at discharge were extracted and exported to STATA version 11 for analysis

Analysis: Descriptive statistics were used to summarize patients' demographics, length of stay, final diagnoses and patient outcomes at discharge. Patients were categorized as having CRD if the final diagnosis made was: Asthma, chronic obstructive pulmonary disease (COPD), Lung cancer or interstitial lung disease/ pneumoconiosis.

Respiratory communicable disease included tuberculosis (all forms), pneumonia, pulmonary Kaposi's sarcoma and pneumocystis carinii/jiroveci pneumonia (PcP/PJP). Patients admitted on the ward with diagnoses other than the above were excluded from this analysis. Patient outcome on discharge were categorized as either alive or dead.

Ethics: Ethical approval to conduct this analysis was sought from Mulago hospital ethics and research committee. Because this was a retrospective analysis individual patients' consent was not obtained. However, all patients consented for the hospital procedures that they underwent at the time of diagnosis.

4.3 RESULTS

From December 2010 through August 2011, a total 568 patients with respiratory diseases were admitted on the pulmonary division ward. Three hundred and thirty (58.2%) were male and 238(41.8%) were females. The mean age was 37.4 years (17.2SD) and ALOS was 5.6 days (8.4SD). The frequencies of the different respiratory diseases encountered on the ward are shown in Table1.

Table 1: Prevalence and outcomes of respiratory disease patients admitted in the Pulmonary Division December 2010-August 2011

Respiratory disease	No. (%)	Died, No. (%)
Asthma	36(6.3)	3(8.3)
COPD	11(1.9)	1(9.3)
Lung cancer	3(0.5)	1(33.3)
Interstitial Lung disease	1(0.2)	0(0.0)
Tuberculosis	266(46.8)	39(14.7)
Pneumonia	243(42.8)	34(14.0)
Pulmonary Kaposi's sarcoma	3(0.5)	1(33.3)
PcP/PJP	5(0.9)	1(20)
Total	568(100)	80(14.1)

Prevalence of CRDs: Fifty one out of the 568 patients (9.0%) admitted patients had a CRD diagnosis. The commonest CRDs were asthma and COPD accounting for 70.6% and 21.6% of all CRD admissions respectively table2.

Patient outcome and average length of stay at discharge: Eighty (14.1%) patients died on the ward. Mortality by different disease conditions is shown in table1.

Five patients (9.8%) of the patients with CRD died while 73 (14.5%) of the patients with communicable respiratory disease. The mean ALOS for chronic respiratory disease was 5.6 days (+/-SD 8.6) and 5.2 days (+/-6.2) for communicable respiratory disease.

Table 2: prevalence and outcomes of CRD patients admitted in the Pulmonary Division ward December 2010-August 2011

Chronic respiratory disease	No. (%)	Died, No. (%)
Asthma	36(70.6)	3(8.3)
COPD	11(21.6)	1(9.1)
Lung cancer	3(5.9)	1(33.3)
Interstitial Lung disease	1(2.0)	0(0.0)
Total	51(100)	5(9.8)

4.4 DISCUSSION

In this retrospective data analysis, the prevalence of CRD was 9.0%. Asthma and COPD were found to be the commonest CRDs in this study as has been reported by studies elsewhere in Africa.⁷⁻⁹ However, the number of admitted asthma patients was lower than reported in other African settings. This could be due to the fact in our hospital many asthma patients are attended to at the emergency ward and discharged before transfer to the ward. COPD numbers could be low because in most cases COPD is

associated with an insidious nature and slow progression, hence only those with severe exacerbations are hospitalized. In addition to this spirometry, the most important test to identify COPD patients was only recently introduced in the hospital.

Infections of the lung are still a major cause of admission with TB and pneumonia accounting for largest proportion of admissions to the ward. Other African hospital studies previously published show similar data.^{7,9} The burden of TB is driven by a high prevalence of HIV as reports from WHO indicate that 39% of Ugandan smear positive patients are HIV infected ¹⁰.

HIV/TB patients are usually very sick. With limited ward space clinicians in the admissions wards triage patients to identify the sickest for in patient care. It is possible that NCD patients may be triaged more for discharge than the TB/HIV patients. In this way creating selection bias towards more TB patients. We also recognize that capacity to diagnose the CRD is low. Limited diagnostic equipment, lack of awareness of the magnitude of these conditions may mean that clinicians may be under diagnosing them.

We found in- hospital asthma mortality of 6.3%. World over mortality from asthma has significantly reduced. ^{11,12} However, asthma morbidity and mortality remain high in Africa. This is possibly due to lack of training in standard asthma management principles coupled with poor access to asthma management guidelines and unavailability of asthma medications among other reasons.¹¹⁻¹³ A recent survey has indicated that clinicians in developing countries do not follow asthma management guidelines.¹⁴

The major limitation of this study is its retrospective design. Data available on the individual patients is limited because it is not captured on the database. Because of this more detailed analysis such as factors associated with mortality, reasons for deterioration to admission especially for CRDs was not possible.

Conclusion: Communicable respiratory diseases still account for the majority of inpatients in Mulago hospital and are associated with high mortality but admission rates and mortality associated with CRD though lower than that of communicable respiratory diseases is higher than in developed settings. There is need for studies that investigate the reasons for admissions and causes of death among patients with CRDs.

Acknowledgements

We are grateful to Mr. Ismail Kaddu for his support during the data management process of this study. Special thanks go to the Head, Department of Medicine Prof. Moses Kanya for encouragement during the conception of this idea. The authors would like to recognize the RASHOTS project that initiated electronic patient data management that allowed easy access to the data used in this analysis

References

1. WHO. Global status report on noncommunicable diseases 2010. 2011.
2. Bloom D, Cafiero E, Jané-Llopis E, Abrahams-Gessel S, Bloom L, Fathima S, et al., editors. The global economic burden of non-communicable diseases. 2011.
3. Nugent R, Feigl AB, Development CfG. Where Have All the Donors Gone?: Scarce Donor Funding for Non-communicable Diseases: Center for Global Development; 2010.
4. Beaglehole R, Bonita R, Alleyne G, Horton R, Li L, Lincoln P, et al. UN high-level meeting on non-communicable diseases: addressing four questions. *The Lancet*. 2011.
5. Organization WH. Global Alliance against Chronic Respiratory Diseases Action Plan 2008-2013. Geneva: WHO. 2008.
6. WHO. Noncommunicable diseases country profiles 2011. 2011.
7. Mboussa J. Respiratory diseases at hospitals in Brazzaville, Congo]. *Revue de pneumologie clinique*. 1990;46(2):61.
8. Steen T, Aruwa J, Hone N. The epidemiology of adult lung disease in Botswana. *The International Journal of Tuberculosis and Lung Disease*. 2001;5(8):775-82.
9. Desalu OO, Oluwafemi JA, Ojo O. Respiratory diseases morbidity and mortality among adults attending a tertiary hospital in Nigeria. *Jornal Brasileiro de Pneumologia*. 2009;35(8):745-52.
10. WHO. Global tuberculosis control: epidemiology, strategy, financing. WHO report. 2011:8.
11. Fuhrman C, Jougla E, Uhry Z, Delmas MC. Deaths with Asthma in France, 2000-2005: A Multiple-Cause Analysis. *Journal of Asthma*. 2009;46(4):402-6.
12. Wilson DH, Tucker G, Frith P, Appleton S, Ruffin RE, Adams RJ. Trends in hospital admissions and mortality from asthma and chronic obstructive pulmonary disease in Australia, 1993-2003. *Medical journal of Australia*. 2007;186(8):408.
13. Aït-Khaled N, Enarson D, Bencharif N, Boulahdib F, Camara L, Dagli E, Djankine K, Keita B, Koadag B, Ngoran K, Odhiambo J, Ottmani S, Pham D, Sow O, Yousser M, Zidouni N. Treatment outcome of asthma after one year follow-up in health centres of several developing countries. *The International Journal of Tuberculosis and Lung Disease*. 2006;10(8):911-6.
14. Aït-Khaled N, Enarson D, Bencharif N, Boulahdib F, Camara L, Dagli E, Djankine K, Keita B, Koadag B, Ngoran K, Odhiambo J, Ottmani S, Pham D, Sow O, Yousser M, Zidouni N. Implementation of asthma guidelines in health centres of several developing countries. *The International Journal of Tuberculosis and Lung Disease*. 2006;10(1):104-9.

CHAPTER 5: Rates of asthma exacerbations and mortality and associated factors in Uganda: a 2-year prospective cohort study

Authors

Bruce J Kirenga^{1,2}, Corina de Jong³, Levicatus Mugenyi^{1,4}, Wincelaus Katagira², Abdallah Muhofa², Moses R Kanya¹, Marike Boezen⁵, Thys van der Molen³

1. Makerere University Lung Institute, Makerere University College of Health Sciences, Kampala, Uganda
2. Department of Medicine, Makerere University College of Health Sciences, Kampala, Uganda
3. GRIAC-Primary Care, department of General Practice and Elderly Care, University of Groningen, University Medical Center Groningen (UMCG), The Netherlands; Groningen Research Institute for Asthma and COPD (GRIAC), University of Groningen, University Medical Center Groningen (UMCG), The Netherlands
4. Center for Statistics, Interuniversity Institute for Biostatistics, and statistical Bioinformatics, UHasselt (Hasselt University), Diepenbeek, Belgium
5. Department of Epidemiology, University of Groningen, Groningen, The Netherlands

Correspondence

Bruce J Kirenga; Makerere University Lung Institute, Mulago Hospital, Mulago Hill Road, P.O. Box 7072, Kampala Uganda, E-Mail: brucekirenga@yahoo.co.uk, Telephone: **+256782404431**

Published in Thorax 2018; 0:1–3.

ABSTRACT

Data on asthma treatment outcomes in Africa is limited. 449 asthmatics (age 5-93 years) in Uganda were followed up for 2 years to determine rates of exacerbations and mortality and associated factors. During follow up the median number of exacerbation per patient was 1 (IQR 0-5) and 17 patients died (3.7%, 27.3 deaths per 1000-person years). Considering only the first year of follow up, 59.6% of the patients experienced at least 1 exacerbation, 32.4% experienced 3 or more exacerbations. A multivariable model showed that the likelihood of experiencing at least 1 exacerbation in the first year of follow up was lower with better baseline asthma control (higher asthma control test (ACT) score), with OR 0.87 (95% CI: 0.82-0.93, $p=0.000$), and was higher with more exacerbations in the year prior to enrolment (OR for log number of exacerbations 1.28 (95% CI: 1.04-1.57, $p=0.018$). Better asthma control OR 0.93 (95% CI: 0.88-0.99, $p=0.021$) and number of baseline exacerbations OR 1.35 (95% CI: 1.11-1.66, $p=0.005$) were also the only factors that were independently associated with experiencing 3 or more exacerbation during the first year of follow up. The only factor found to be associated with all-cause mortality was FEV₁, with higher recent FEV₁ associated with lower all-cause mortality (OR 0.30 (95% CI: 0.14 – 0.65; $p=0.002$). Rates of asthma exacerbations and mortality are high in Uganda and are associated with poor asthma control. Health systems should be strengthened to care for asthma patients.

Key words: Asthma, exacerbations, mortality, Uganda

5.1 BACKGROUND

Asthma exacerbations and mortality are the worst asthma treatment outcomes.¹ Asthma exacerbations are responsible for most asthma morbidity, health care utilization, poor quality of life and precede most asthma deaths.² Some patients experience frequent asthma exacerbations (defined usually as experiencing ≥ 3 exacerbations in a year). These patients have been described as having an exacerbation-prone asthma phenotype in some literature³ and are at the greatest risk of adverse asthma outcomes including death. The risk factors for exacerbations include low use of inhaled corticosteroids, allergic rhinitis, seasonal changes, gastroesophageal disease, psychosocial factors, recurrent chest infections, aspirin intolerance, cigarette smoking, non-adherence to medications, obesity and higher number of exacerbations in the past year.³

Globally, asthma mortality is estimated at 0.19/100000 population.⁴ According to a recent analysis of asthma mortality in 46 countries, asthma mortality rates were observed to be decreasing in the 1990s through the 2000s but have recently stagnated.⁴ Asthma mortality rate was 0.44 deaths per 100 000 people in 1993 and reduced to 0.19 deaths per 100 000 people in 2006 but no significant change was observed between 2006 and 2012.⁴ There are significant disparities in asthma mortality between countries, with low and middle-income countries having the highest number of asthma deaths. Risk factors for asthma mortality include: older age, gender, African race, low use of inhaled corticosteroids (ICS), inappropriate use of long acting beta agonists, fixed airway obstruction (lack of reversibility), previous exacerbation, low FEV₁ and psychological and psychosocial factors.⁵

Data on asthma exacerbations and mortality and their predictors in Africa is severely limited. We therefore set up this prospective cohort study called the Uganda Registry for Asthma and chronic obstructive pulmonary disease (COPD) (URAC) to document the rates of asthma exacerbations and mortality and their predictors in Uganda.

5.2 METHODS

URAC is conducted in the chest clinics of 6 tertiary hospitals in Uganda namely Mulago hospital, Mbarara hospital, Mbale hospital, Hoima hospital, Arua hospital and Gulu hospital. For the current analysis, only patients enrolled at Mulago hospital are included. The Mulago Hospital Research and Ethics committee and the Uganda National Council for Science and Technology approved this study. All asthma patients who were 5 years and older and provided consent were enrolled and followed up every six months for two years. Using a standardized clinical record form (CRF), data on patients' socio-demographics, clinical and lung function were collected. Asthma control was measured at each visit using the Asthma Control Test (ACT). All patients underwent spirometry according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines using a Pneumotrac[®] spirometer with Spirotrac[®] V software (Vitalograph Ltd., Buckingham, United Kingdom). Predicted parameters were based on NHANES III models for African Americans. Asthma medications prescriptions were based on GINA guidelines.

Median number of exacerbations per patient over the entire 2 years follow up period was calculated. The proportions of patients experiencing ≥ 1 exacerbation and ≥ 3 exacerbations during the first year of follow up was calculated. First data on exacerbations was considered in order to avoid recall bias and because of high attrition rate (32.5%) and the fact that less than 50% of the cohort could be followed

up by this time. Exacerbations were defined according to the ATS/ERS definitions. Death was by postmortem reports and verbal autopsy and all-cause mortality was considered. Incidence of death was calculated as number of deaths during the total follow up period divided by total follow up time in years. Factors associated with all-cause mortality were analyzed using the Cox Proportional Hazards model with age at death used as survival time variable while factors associated with exacerbations (≥ 1 and ≥ 3 exacerbations per year) were determined using logistic regression.

5.3 RESULTS

From August 13th 2013 to April 24th, 2016, 449 asthma patients (28.3% male, median age 33 years (IQR 20-48)) were enrolled into the URAC registry at Mulago Hospital. Patients socio-demographic characteristics are presented in Table 1. At baseline, 32.2% of the patients had controlled asthma and 33.0% had evidence of airflow obstruction on spirometry (i.e. had FEV₁/FVC ratio < 0.70). Smoking was reported by 12% of the patients, HIV by 6%, history of tuberculosis treatment by 6.2%, nasal congestion by 88.2% and heartburn by 60.6%. A total of 147 (32.7%) of the patients were on ICS either ICS alone or ICS/LABA at baseline.

Table 1: Baseline patients' characteristics

Characteristic	Number	Percentage
Male gender	127	28.3
Age groups		
<15	54	12.0
15-24	87	19.4
25-34	91	20.3
35-44	83	18.5
45-54	60	13.4
55-64	38	8.5
65+	36	8.0
Respiratory Symptoms		
Cough	379	84.4
Sputum	214	47.7
Wheezing	434	96.7
Shortness of breath	436	97.0
Lung Function abnormalities		
FEV ₁ /FVC ratio <0.70	148	33.0
FEV ₁ % 50%-79% predicted	163	36.3
FEV ₁ % 30%-49% predicted	58	12.9
FEV ₁ % <30% predicted	17	3.8
Asthma control		
Uncontrolled, ACT <15	126	28.1
Partially controlled, 15≤ACT≤19	174	38.8
Controlled, ACT>19	149	33.2
Medications		
Salbutamol inhaler	318	70.8
Inhaled corticosteroids	83	18.5
Combination inhalers (steroid, LABA)	64	14.3
Leukotriene modifiers	66	14.7
Risk factors and co-morbid conditions		
History of smoking	54	12.0
Exposure to bio-mass†	390	86.9
Ever been treated for TB	28	6.2
HIV Positive	27	6.0
Nasal congestion or rhinorrhea	396	88.2
Heart burn/acid irritation	272	60.6

†Including use of wood, charcoal and kerosene for cooking or lighting, ACT=asthma control test, LABA=long acting beta agonist

Exacerbations

The proportion of patients who experienced ≥ 1 exacerbation the first year was 59.6% (268) while 32.4% (133) experienced ≥ 3 exacerbations in the first year. At bivariate level experiencing at least 1 exacerbation in the first year was associated with respiratory rate OR 2.58 (95% CI: 1.01 – 6.57, $p=0.047$), having used inhaled corticosteroids prior to the clinic visit OR 2.93 (95% CI: 1.56 – 5.48, $p=0.001$), number of baseline exacerbations OR 1.47 (95% CI: 1.21 – 1.79, $p<0.001$), asthma control test (ACT) scores OR 0.89 (95% CI: 0.85 – 0.94, $p<0.001$) and FEV₁ OR 0.56 (95% CI: 0.35 – 0.89, $p=0.014$) while experiencing 3 or more exacerbations was associated with age OR 1.71 (95% CI: 1.17

– 2.50); $p=0.006$), number of baseline exacerbations OR 1.48 (95% CI: 1.22 – 1.79; $p<0.001$), having used inhaled corticosteroids prior to the clinic visit 1.96 (95% CI: 1.14 – 3.35; $p=0.014$), respiratory rate 2.14 (95% CI: 1.04 – 4.40; $p=0.039$), ACT scores OR (95% CI: 0.84; 0.79 – 0.89; <0.001), FEV_1 OR 0.64 (95% CI: 0.41 – 0.99; $p=0.044$) and FEV_1/FVC ratio OR 0.11 (95% CI: 0.03 – 0.46, $p=0.011$) and exposure to biomass smoke exposure 0.54 (95% CI: 0.30 – 0.99; $p=0.048$).

At multivariate analysis the only factors independently associated with experiencing at least 1 exacerbation in the first year of follow up were ACT score OR 0.87 (95% CI: 0.82-0.93, $p=0.000$) and number of baseline exacerbations OR 1.28 (95% CI: 1.04-1.57, $p=0.018$). ACT score OR 0.93 (95% CI: 0.88-0.99, $p=0.021$) and number of baseline exacerbations OR 1.35 (95% CI: 1.11-1.66, $p=0.005$) were also the only factors independently associated with experiencing 3 or more exacerbation during the first year of follow up.

Mortality

Overall 17 patients died (3.7%), 11 (64.7%) from circumstances judged to be asthma related (online supplementary table 2). The incidence of all-cause mortality was 27.3 per 1000-person years, male vs. female, 34.2 vs. 24.6, incidence death rate ratio 1.39 (0.42-4.09) and increased with increasing age, supplementary Table 1. At bivariate analysis, all-cause mortality was associated with FEV_1 and FVC (adjusted hazards ratio, 0.30; 0.14 – 0.65; $p=0.002$ and (0.28; 0.12 – 0.68, $p=0.005$) respectively while history of tuberculosis treatment (adjusted hazard ratio 3.10; 1.00-9.65; $p=0.051$) and use of herbs (adjusted hazard ratio 3.86; 0.99-15.04; $p=0.052$) were associated higher mortality but only as a trend (Table 2). At multivariate analysis only FEV_1 remained independently associated with all-cause mortality HR 0.30 (95% CI: 0.14-0.65, $p=0.002$).

Table 2. Factors associated with exacerbations and all-cause mortality at multivariate analysis

Factor	OR (95% CI)	p-value
≥1 exacerbation/year		
ACT score	0.87 (0.82-0.93)	$p=0.000$
Number of baseline exacerbations [‡]	1.28 (1.04-1.57)	$p=0.018$
≥3 exacerbation/year		
ACT score	0.93 (0.88-0.99)	0.021
Number of baseline exacerbations [‡]	1.35 (1.11-1.66)	0.005
All-cause mortality		
Recent FEV_1 [‡]	0.30 (0.14 – 0.65)	0.002

[‡] log transformed because of skewness, interpretation should be done at the log scale, note: analysis considers only the first year of follow up

5.4 DISCUSSION

Our study has shown that 59.6% of asthma patients experience at least one exacerbation in a year, 32.4% experience ≥3 exacerbations in a year and the all-cause mortality rate is 3.7% (27.3 per 1000-person years). Exacerbations were less likely with better baseline asthma symptom control and more likely with higher number of baseline exacerbations. Mortality was lower with higher recent FEV_1 .

The rates of exacerbations and mortality observed in this study are much higher than the rates observed

in developed settings and higher than the 1% asthma mortality rate for Uganda reported in the global burden of disease report.⁴⁻⁸ For example De Marco et al reported a mortality incidence rate of only 1.1/1000 person years in a cohort of Italian young adults (20-44 years) followed up for seven years.⁷ Although our 27.3/1000-person years found in our cohort could be because we report all-cause mortality while the De Marco study reported asthma specific mortality, the 27-fold higher mortality rate we observed in this study indicates that asthma mortality rates in Uganda is very high. The associations between exacerbations and mortality with asthma control, number of baseline exacerbations and FEV₁ have been previously reported.^{5, 7} Both the ACT and FEV₁ are measures of asthma control; ACT uses symptoms, medication use and work impairment to assess asthma control while FEV₁ is an objective measure of the severity of airflow obstruction, a component of asthma control. Therefore, the grim asthma treatment outcomes in this study are most likely a reflection of uncontrolled asthma due to limited access to asthma treatment in our setting. The higher rates may also be race related, since the African race has been found to be associated with more severe asthma.⁹ The lack of use of recommended asthma medications particularly ICS in this cohort calls for efforts to increase availability and affordability of asthma medication since increased access to medicines has been reported to result into better asthma treatment outcomes in some settings such as the case of Brazil where hospitalizations were significantly reduced with increased access to medications.¹⁰ In conclusion, the rates of asthma exacerbations and mortality observed in this study are very high and require strengthening of the health systems to improve asthma care in Uganda.

Acknowledgments

The authors wish to thank the patients who participated in the study. We specifically thank Mr. Rogers Sekibira who managed the data. We thank the study nurses, administrators and the management of Mulago Hospital and Makerere University for facilitating different aspects of the study. Finally, we thank Wide spectrum Uganda for funding the pilot Uganda Registry for Asthma and COPD (URAC) which formed the basis for obtaining the funding from the GSK Trust In Science Africa.

Competing Interests

All authors declare no competing interests for this article

Funding

This study was funded by the GSK's Trust In Science Africa Project

Contributorship

Bruce Kirenga conceived the idea of the project and wrote the initial proposal. Thys van der Molen, Moses Kamywa and Marike Boezen critically advised the writing of the proposal. Corina de Jong and Levi Mugenyi supported data analysis. Wince Katagira and Abdallah Muhofa performed patient clinical reviews. All authors critically reviewed and contributed to manuscript writing.

References

1. 2017 GINA Report, Global Strategy for Asthma Management and Prevention. [cited 2017 June 25]; Available from: <http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/>
2. Lane S, Molina J, Plusa T. An international observational prospective study to determine the cost of asthma exacerbations (COAX). *Respiratory medicine*. 2006; 100(3): 434-50.
3. Dougherty R, Fahy JV. Acute exacerbations of asthma: epidemiology, biology and the exacerbation-prone phenotype. *Clinical & Experimental Allergy*. 2009; 39(2): 193-202.
4. Ebmeier S, Thayabaran D, Braithwaite I, Bénamara C, Weatherall M, Beasley R. Trends in international asthma mortality: analysis of data from the WHO Mortality Database from 46 countries (1993–2012). *The Lancet*. 2017; 390(10098): 935-45.
5. Ali Z, Dirks CG, Ulrik CS. Long-term mortality among adults with asthma: a 25-year follow-up of 1,075 outpatients with asthma. *Chest Journal*. 2013; 143(6): 1649-55.
6. Schatz M, Meckley LM, Kim M, Stockwell BT, Castro M. Asthma exacerbation rates in adults are unchanged over a 5-year period despite high-intensity therapy. *The Journal of Allergy and Clinical Immunology: In Practice*. 2014; 2(5): 570-4. e1.
7. De Marco R, Locatelli F, Cazzoletti L, Bugianio M, Carosso A, Marinoni A. Incidence of asthma and mortality in a cohort of young adults: a 7-year prospective study. *Respiratory research*. 2005; 6(1): 95.
8. Global Burden of Disease Visualisations: Cause of Death. [cited 2017 December 14]; Available from: <http://www.thelancet.com/lancet/visualisations/cause-of-death>
9. Gamble CM. Racial Disparities in Asthma Severity: a Comparison Between Black and White Adult Asthmatics in the Severe Asthma Research Program. University of Pittsburgh; 2011.
10. Comaru T, Pitrez PM, Friedrich FO, Silveira VD, Pinto LA. Free asthma medications reduces hospital admissions in Brazil (Free asthma drugs reduces hospitalizations in Brazil). *Respiratory medicine*. 2016; 121: 21-5.

5.5 Online supplemental material for the manuscript “Rates of asthma exacerbations and mortality and associated factors in Uganda: a 2-year prospective cohort study.”

Bruce J Kirenga^{1,2}, Corina de Jong³, Levicatus Mugenyi^{1,4}, Wincellaus Katagira², Abdallah Muhofa², Moses R Kamya¹, Marike Boezen⁵, Thys van der Molen³

1. Makerere University Lung Institute, Makerere University College of Health Sciences, Kampala, Uganda
2. Department of Medicine, Makerere University College of Health Sciences, Kampala, Uganda
3. GRIAC-Primary Care, department of General Practice and Elderly Care, University of Groningen, University Medical Center Groningen (UMCG), The Netherlands; Groningen Research Institute for Asthma and COPD (GRIAC), University of Groningen, University Medical Center Groningen (UMCG), The Netherlands
4. Center for Statistics, Interuniversity Institute for Biostatistics, and statistical Bioinformatics, UHasselt (Hasselt University), Diepenbeek, Belgium
5. Department of Epidemiology, University of Groningen, Groningen, The Netherlands

Correspondence

Bruce J Kirenga; Makerere University Lung Institute, Mulago Hospital, Mulago Hill Road, P.O. Box 7072, Kampala Uganda, E-Mail: brucekirenga@yahoo.co.uk, Telephone: **+256782404431**

5.5.1 METHODS

Design and setting

URAC is a prospective cohort study of asthma and chronic obstructive pulmonary disease (COPD) patients in Uganda. Enrollment into this registry started in August 2013 and continues. Asthma and COPD patients diagnosed in the chest clinics of 6 tertiary hospitals in Uganda namely Mulago hospital, Mbarara hospital, Mbale hospital, Hoima hospital, Arua hospital and Gulu hospital are enrolled into this registry. For the current analysis only, patients enrolled at Mulago hospital are included. Mulago hospital is the national referral hospital of Uganda, situated in the heart of Kampala, the capital city of Uganda. The hospital has a bed capacity of 1500 beds.

Study procedures

Asthma diagnosis: Diagnosis of asthma is made by attending physicians in the respective chest clinics. Once a diagnosis of asthma is made, patients undergo spirometry at the registry clinic. Asthma patients who have fixed airflow obstruction (i.e. their FEV_1 does not increase by $\geq 12\%$ (and $\geq 200\text{ml}$) after administration of $400\mu\text{g}$ of salbutamol) are excluded and registered as having COPD.

Patients who are referred for registration as having COPD who have reversible airflow obstruction are registered as asthma patients. Spirometry is conducted and interpreted according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines using a Pneumotrac[®] spirometer with Spirotrac[®] V software (Vitalograph Ltd., Buckingham, United Kingdom).³ Predicted parameters are based on NHANES III models for African Americans.⁴

Registration into the registry and follow up: All asthma patients diagnosed in the chest clinics are reviewed by a dedicated registry medical officer for enrollment into the registry. A clinical record form (CRF) is used to collect the following baseline data: socio-demographics, asthma risk factors, respiratory symptoms and signs, vital signs, anthropometry, spirometry, number of exacerbations, visits to health facilities and hospitalization due to respiratory symptoms in years preceding the registration, asthma medications use and asthma control assessed with the asthma control test (ACT¹). Patients are followed up every six months and each visit the following data is collected: respiratory symptoms and signs, vital signs, anthropometry, spirometry, number of exacerbations, visits to health facilities and hospitalization due to respiratory symptoms since the last visit, asthma medications use and asthma control assessed by ACT¹

Patient management: Dedicated registry clinicians and nurses review all enrolled patients. The registry clinicians have received asthma management training by the investigators according to GINA guidelines and prescriptions are made according to GINA guidelines.⁵ During registry visits the medical officer can prescribe and advise treatment according to his discretion. The registry does not provide medication to patients or any incentives such as transport refund. Patients continue to obtain their asthma medications from the hospital pharmacy or other sources such as private pharmacies. The registry nurse reminds patients of their next follow up visits (follow ups are every six months) and patients who miss visits are contacted by telephone to encourage them to attend the clinic. Patients also continue to attend their regular chest clinic visits as required by their attending physicians. A follow-up CRF is used at each visit to collect data on respiratory symptoms, asthma exacerbations, asthma medications used since the previous visit, ACT, and spirometry data.

Asthma exacerbations: In this study, an exacerbation was defined according to the ATS/ERS definition as “events characterized by a change from the patient’s previous status”.⁶ We considered only exacerbations that required a patient to either visit a health facility or to be hospitalized (i.e. moderate to severe exacerbations) as recommended by the ATS/ERS guidelines.⁶

Mortality data collection: All-cause mortality data is collected, attempts are made to establish cause of death. For patients who die in hospital we obtain data on the cause of death from hospital charts or postmortem reports if available. If a patient dies outside the hospital the registry team uses a verbal autopsy form (developed according World Health Organization (WHO) guidelines⁷) to collect circumstances surrounding death and the possible cause of death from relatives or care takers. A period of two weeks is allowed after death for the verbal autopsy interview.

Statistical analysis

Patients baseline socio-demographic, clinical and lung function characteristics were summarized as proportions. For continuous variables, mean or median plus standard deviation and interquartile range are presented, depending on data normality.

The proportion of patients experiencing at least one exacerbation was calculated as well as the proportion of patients with ≥ 3 exacerbations in a year and stratified by gender and age group. Incidence of death was calculated as number of deaths during the total follow up period divided by total follow up time in years. Incidence rates were also stratified by gender and age group.

To determine factors associated with all-cause mortality, survival analysis using Cox Proportional Hazards model was used with age at death considered the survival time. Hazard Ratios (HR) for death are presented along with their 95% confidence intervals (95% CI). Factors associated with experiencing at least 1 or ≥ 3 exacerbations per year were determined using logistic regression, by defining a binary outcome as 1 if one had ≥ 3 exacerbations per year at least once during the first year of follow-up and zero if otherwise. Firstly, each factor was regressed separately and then factors with P values less than or equal to 0.20 were subjected to multiple logistic regression. For the Cox regression, no adjusted estimates were produced since only one factor (recent FEV₁) was independently associated with death. To arrive at a better fit for the logistic regression, backward model building was conducted using the likelihood ratio test (LRT). In addition, a better fit was checked for multicollinearity problems using the variance inflation factor (VIF). In case multicollinearity existed (VIF>10), centering of continuous variables was considered, else variables with less significance or scientific meaning were dropped.

Ethics

Ethics approval was obtained from the Mulago Hospital Research and Ethics committee and the Uganda National Council for Science and Technology. Participants provided written informed consent and were free to terminate study participation at any time during the study. For children aged 5-7 years parental/guardian consent was obtained while for children between the ages of 8-18 years we obtained their assent and parental/legal guardian consent.

5.5.2 RESULTS

Asthma medication use

We recorded medications patients were taking for the treatment of asthma at baseline and at each follow up visit. The trajectories of the different medications use at baseline and during follow up are shown in supplementary figure 1. At baseline use of any inhaled corticosteroid (ICS) either as standalone ICS or in combination with a long acting beta agonist (ICS/LABA) inhalers, salbutamol inhaler, oral prednisolone, leukotriene modifiers tablets, salbutamol tablets/salbutamol syrups, aminophylline tablets, antibiotics and herbs were 32.7%, 70.8%, 78.2%, 14.7%, 73.1%, 48.8%, 91.3% and 18.9% respectively. The proportion of patients on any ICS increased to 34.3% by month six of follow up and dropped to 12.9% by month 24 of follow up.

ICS=inhaled corticosteroids

Supplementary Figure 1. Trajectory of asthma medications use in the study among study patients

Relationship between all-cause mortality and frequent exacerbations (≥ 3 /year)

A total of 17 patients died overall and 133 (32.4%) patients experienced 3 or more exacerbations in a year. Twelve of the 17 patients who died (70.6%) were in the group who experienced 3 or more exacerbations; 4 of these deaths were judged to be due to other causes other than asthma (one was due

to stroke, one due to heart failure, one due to intestinal obstruction and one due to anaemia). Figure 2 below

Supplementary Figure 2. Kaplan Meier plot of all-cause mortality rates by frequent exacerbation category

Supplementary tables

Supplementary Table 1 Rates of experiencing ≥ 3 exacerbations per year and mortality among study participants stratified by gender and age group

	Experienced ≥ 3 exacerbations per year		all-cause Mortality			
Group	Number of asthmatics N (%)	Rate ratio 95% CI	Number of deaths N (%)	Person years	Incidence rate [‡] (deaths per 1000 years) 95% CI	Incidence rate ratio 95% CI
Overall	133 (32.4)		17 (100)	622.0	27.3 (17.0-44.0)	
Gender						
Male	32 (27.6)	0.8 (0.6 –1.1)	6 (35.3)	175.6	34.2 (15.3-76.0)	1.39 (0.42-4.09)
Female	101 (34.2)	1	11 (64.7)	446.4	24.6 (13.6-44.5)	1
Age group						
<15	11 (21.2)	0.6 (0.3 –1.3)	0 (0.0)	74.0	0.0 (---)	0.0 (---)
15-24	26 (32.9)	0.9 (0.5 –1.8)	2 (11.8)	115.9	17.3 (4.3-69.0)	0.09 (0.01-0.49)
25-34	18 (21.4)	0.6 (0.3 –1.2)	1 (5.9)	122.3	8.2 (1.2-58.0)	0.04 (0.00 –0.34)
35-44	27 (34.2)	1.0 (0.5 –1.9)	4 (23.5)	126.3	31.7 (11.9-84.4)	0.17 (0.04-0.67)
45-54	26 (44.8)	1.3 (0.7 –2.4)	2 (11.8)	93.3	21.4 (5.3-85.7)	0.11 (0.01-0.60)
55-64	17 (47.2)	1.4 (0.7 –2.6)	1 (5.9)	52.7	19.0 (2.7-134.6)	0.10 (0.00-0.79)
65+	8 (34.8)	1	7 (41.2)	37.5	186.7 (88.9-391.2)	1

[‡] Number of deaths divided by person years [†]Year 1 and 2

Supplementary Table 2. Results of bivariate analysis of factors associated with exacerbations and all-cause mortality

Factor	≥1 exacerbation/year		≥3 exacerbation/year		All-cause mortality	
	OR (95% CI)	p-value	OR (95% CI)	p-value	HR (95% CI)	p-value
Age (years) [‡]	1.08 (0.77 – 1.51)	0.665	1.71 (1.17 – 2.50)	0.006		
Gender: male	0.74 (0.48 – 1.14)	0.170	0.73 (0.46 – 1.17)	0.195	0.65 (0.22 – 1.98)	0.452
ACT score	0.89 (0.85 – 0.94)	<0.001	0.84 (0.79 – 0.89)	<0.001	1.36 (0.50 – 3.66)	0.544
Ever been treated for TB	1.30 (0.57 – 2.99)	0.536	0.76 (0.31 – 1.85)	0.541	3.10 (1.00 – 9.65)	0.051
HIV status						
Positive	Reference		Reference		Reference	
Negative	0.79 (0.34 – 1.83)	0.585	0.89 (0.38 – 2.06)	0.786	0.88 (0.11 – 6.91)	0.902
Unknown	0.49 (0.15 – 1.53)	0.218	1.01 (0.31 – 3.27)	0.990	2.26 (0.23 – 22.17)	0.484
Nasal congestion or rhinorrhea	0.94 (0.50 – 1.77)	0.854	0.79 (0.42 – 1.50)	0.480	1.91 (0.25 – 14.55)	0.531
Heart burn/acid irritation	1.28 (0.85 – 1.91)	0.233	1.23 (0.80 – 1.90)	0.335	0.94 (0.34 – 2.59)	0.907
Recent use of ICS	2.93 (1.56 – 5.48)	0.001	1.96 (1.14 – 3.35)	0.014	0.58 (0.20 – 1.68)	0.314
Recent BMI [‡]	1.10 (0.50 – 2.42)	0.808	1.74 (0.76 – 3.97)	0.189	0.49 (0.05 – 4.62)	0.534
Recent respiratory rate [‡]	2.58 (1.01 – 6.57)	0.047	2.14 (1.04 – 4.40)	0.039	0.84 (0.09 – 7.56)	0.873
Recent SPO2	0.95 (0.89 – 1.02)	0.167	0.98 (0.93 – 1.03)	0.432	0.96 (0.87 – 1.05)	0.369
Number of baseline exacerbations [‡]	1.47 (1.21 – 1.79)	<0.001	1.48 (1.22 – 1.79)	<0.001	1.10 (0.72 – 1.67)	0.668
Recent FEV1 [‡]	0.56 (0.35 – 0.89)	0.014	0.64 (0.41 – 0.99)	0.044	0.30 (0.14 – 0.65)	0.002
Recent FEV ₁ /FVC ratio	0.52 (0.17 – 1.62)	0.259	0.11 (0.03 – 0.46)	0.011	0.53 (0.02 – 16.32)	0.718
Recent FVC [‡]	0.58 (0.33 – 1.03)	0.064	0.79 (0.45 – 1.40)	0.424	0.28 (0.12 – 0.68)	0.005
History of smoking	0.86 (0.47 – 1.57)	0.614	1.58 (0.85 – 2.92)	0.145	0.50 (0.11 – 2.23)	0.363
Exposure to bio-mass	0.69 (0.36 – 1.29)	0.242	0.54 (0.30 – 0.99)	0.048	0.73 (0.20 – 2.61)	0.626
Recent use of herbs	2.09 (0.66 – 6.58)	0.210	2.16 (0.79 – 5.89)	0.132	3.86 (0.99 – 5.04)	0.052
Reversibility [‡]	1.19 (0.93 – 1.52)	0.158	1.04 (0.81 – 1.34)	0.735	0.87 (0.50 – 1.51)	0.612

[‡] log transformed because of skewness, interpretation should be done at the log scale, note: analysis considers only the first year of follow up

Supplementary Table 3. Circumstances surrounding death for each individual patient who died and probable causes of death

Serial No.	Circumstances surrounding death	P r o b a b l e cause of death	Exacerbation group(≥ 3 , <3)
1	Admitted with cough, wheezing and failure to breath for 2 days.	Asthma	≥ 3
2	Got an attack, failed to breath and died on administration of oxygen in hospital.	Asthma	≥ 3
3	Admitted to heart institute with body swelling, developed headache, and later died.	Kidney failure/or heart failure	<3
4	Developed an attack and passed on at home	Asthma	≥ 3
	She developed an attack and passed on at home.	Asthma	<3
5	Developed respiratory problems and died	Asthma	<3
6	Developed cough and fast breathing, had a high blood pressure, got a stroke, then passed on	stroke	≥ 3
7	Suddenly developed an attack & died shortly afterwards.	Asthma	≥ 3
8	Developed an attack and died shortly afterwards	Asthma	≥ 3
9	Developed an asthmatic attack after 3weeks of discharge and passed away.	Asthma	≥ 3
10	Developed a severe asthma attack at home and shortly passed away	Asthma	≥ 3
11	Had body swelling and died	Heart failure.	<3
12	Had progressively worsening of chest pain and difficulty in breathing and suddenly stopped breathing	Heart failure or cardiac cause	≥ 3
13	Had no respiratory symptoms but developed abdominal distension and died on arrival in the hospital	Intestinal obstruction	≥ 3
14	Suddenly got an attack and died afterwards	Asthma	<3
15	Developed cough & fast breathing was rushed to a clinic where death occurred	Asthma	≥ 3
16	Had recurrent anemia	Anemia	≥ 3

References

1. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. *Journal of Allergy and Clinical Immunology*. 2004; 113(1): 59-65.
2. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *European Respiratory Journal*. 2005; 26(2): 319-38.
3. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *American journal of respiratory and critical care medicine*. 1999; 159(1): 179-87.
4. Global Strategy for Asthma Management and Prevention (2016 update). [cited 2017 April 18]; Available from: ginasthma.org/wp-content/uploads/2016/04/GINA-2016-main-report_tracked.pdf
5. Reddel HK, Taylor DR, Bateman ED, Boulet L-P, Boushey HA, et al. An official american thoracic society/european respiratory society statement: Asthma control and exacerbations: Standardizing endpoints for clinical asthma trials and clinical practice. *American journal of respiratory and critical care medicine* 2009; 180:59-99.
6. WHO. International Standard Verbal Autopsy Questionnaires. Verbal autopsy standards: ascertaining and attributing cause of death Geneva: WHO Press pp 34-51. 2007.

CHAPTER 6: The impact of HIV on the prevalence of asthma in Uganda: a general population survey

Authors

Bruce J. Kirenga,^{1,3} Levicatus Mugenyi,^{3,4} Corina de Jong,² J. Lucian Davis,⁷ Wincelaus Katagira,³Thys van der Molen,² Moses R. Kanya,⁶ and Marika Boezen⁵

1. Pulmonology Unit, Department of Medicine, Makerere University College of Health Sciences, Kampala, Uganda; Email: brucekirenga@yahoo.co.uk
2. GRIAC-Primary Care, department of General Practice and Elderly Care, University of Groningen, University Medical Center Groningen (UMCG), The Netherlands; Groningen Research Institute for Asthma and FIXED AIRFLOW OBSTRUCTION (GRIAC), University of Groningen, University Medical Center Groningen (UMCG), The Netherlands; Email: c.de.jong02@umcg.nl
3. Makerere University Lung Institute, Makerere University College of Health Sciences, Kampala, Uganda; Email: wincegira@gmail.com
4. Center for Statistics, Interuniversity Institute for Biostatistics and statistical Bioinformatics, UHasselt (Hasselt University), Diepenbeek, Belgium; Email: lmugenyi005@gmail.com
5. Department of Epidemiology, University of Groningen, Groningen, The Netherlands, h.m.boezen@umcg.nl
6. Moses R Kanya, Department of Medicine, Makerere University College of Health Sciences, Kampala, Uganda; Email: mkamaya@infocom.co.ug
7. Department of Epidemiology of Microbial Diseases, Yale School of Public Health, and Pulmonary, Critical Care, and Sleep Medicine Section, Yale School of Medicine, New Haven, CT; Email: lucian.davis@yale.edu

Corresponding author: Bruce J Kirenga; E-Mail: brucekirenga@yahoo.co.uk, Telephone: +256782404431

Published in **Respiratory Research (2018) 19:184**

ABSTRACT

Background: HIV and asthma are highly prevalent diseases in Africa but few studies have assessed the impact of HIV on asthma prevalence in high HIV burden settings. The objective of this analysis was to compare the prevalence of asthma among persons living with HIV (PLHIV) and those without HIV participating in the Uganda National Asthma Survey (UNAS).

Methods: UNAS was a population-based survey of persons aged ≥ 12 years. Asthma was diagnosed based on either self-reported current wheeze concurrently or within the prior 12 months; physician diagnosis; or use of asthma medication. HIV was defined based on confidential self-report. We used Poisson regression with robust standard errors to estimate asthma prevalence and the prevalence ratio (PR) for HIV and asthma.

Results: Of 3416 participants, 2067 (60.5%) knew their HIV status and 103 (5.0%) were PLHIV. Asthma prevalence was 15.5% among PLHIV and 9.1% among those without HIV, PR 1.72, (95%CI 1.07-2.75, $p=0.025$). HIV modified the association of asthma with the following factors, PLHIV vs. not PLHIV: tobacco smoking (12% vs. 8%, $p<0.001$), biomass use (11% vs. 7%, $p<0.001$), allergy (17% vs. 11%, $p<0.001$), family history of asthma (17% vs. 11%, $p<0.001$), and prior TB treatment (15% vs. 10%, $p<0.001$)

Conclusion: In Uganda the prevalence of asthma is higher in PLHIV than in those without HIV, and HIV interacts synergistically with other known asthma risk factors. Additional studies should explore the mechanisms underlying these associations. Clinicians should consider asthma as a possible diagnosis in PLHIV presenting with respiratory symptoms.

Key words

Asthma, HIV, prevalence, Uganda

6.1: BACKGROUND

Human Immunodeficiency Virus (HIV) and asthma are both highly prevalent diseases globally.^{1, 2} An estimated 334 million people have asthma and 36.7 million people have HIV.^{1, 2} Both diseases disproportionately affect Africa and other low- and middle-income countries (LMICs).^{2, 3} The weighted mean prevalence of asthma in Africa is 7.0% in the rural areas (2.5-11.5) and 9.6% (3.9-15.2) in urban areas. The prevalence of asthma and HIV in Uganda is 10% and 6.2% respectively.^{4, 5}

Epidemiological studies have found increased prevalence of asthma among HIV infected persons.⁶⁻¹³ However, the number of studies is small and most are either clinical or hospital based and most of them have been conducted in high income low HIV burden settings. Examples of available studies include a study that included 248 HIV infected and 236 HIV uninfected males. This study found that the prevalence of wheezing was 54.4%, vs. 21.2%, $p < 0.001$ (9). In another study among 223 HIV patients in the USA, the prevalence of doctor diagnosed asthma was 20.6 compared to 8.2% in the general population.¹³ In a study comparing 14,005 HIV infected with age matched HIV uninfected controls in Canada, the prevalence ratio for asthma was 1.31 (95% CI 1.20-1.43).¹²

Several mechanisms through which HIV increases the prevalence of asthma have been proposed.¹⁴⁻¹⁶ Notable among these is the HIV associated persistent immune activation and inflammation.¹⁷ It is also postulated that HIV proteins such as the nef protein or activation of memory CD4 T cells directly increase the risk of asthma.¹⁸ Studies indicate that the higher the viral loads, the worse the lung function in HIV infected populations.^{14, 17} HIV infected persons have been found to have higher levels of Immunoglobulin E (IgE) and this increases with increasing immunosuppression.¹⁵ IgE is a well-known mediator of allergy and asthma. HIV could also drive asthma through its association with predominance of T-helper 2 (Th2) pathway. Priming of the Th2 pathway is known to increase the risk of asthma and other allergic diseases.^{19, 20} In a cohort of 223 HIV infected persons, doctor diagnosed asthma appeared to be more common in participants with high sputum interleukin 4 (IL-4) (27% with asthma if high IL-4 vs. 10.5% with asthma if low IL-4, $p = 0.02$).¹³ Antiretroviral therapy (ART) medications used to treat HIV have also been implicated in increasing the risk of asthma among HIV infected persons.²¹

An interaction between HIV and asthma is important in high HIV burden settings because with the availability of highly active antiretroviral therapy and efficient health systems to deliver them, many HIV infected people are living longer into age groups where non-communicable diseases (NCDs) are common. In addition, prevention of HIV may lead to reduction in the burden of asthma. Data on the burden of asthma in HIV may also lead to assessment of asthma in HIV and routine HIV testing among persons with asthma. Drug-drug interactions in the management of patients with asthma-HIV comorbidity is also a key consideration.

In this study we analyzed data from the Uganda national asthma survey (UNAS) to determine if the prevalence of asthma was higher among persons with self-reported HIV infection. We also aimed to determine if HIV interacts with other known asthma risk factors namely tobacco smoking, biomass use, TB, family history of asthma and allergy.

6.2 METHODS

Design and study participants

UNAS was a cross sectional general population-based survey conducted in Uganda in 2016. Participants were selected in clusters (villages) selected by probability proportionate to size by the Uganda Bureau of Statistics using the Uganda National population and housing census of 2014. Households (HHs) within clusters were selected by simple random sampling from a HH list generated by village leaders. All persons aged ≥ 12 years who were members of selected HH and provided written informed consent (and assent in case of minors) were surveyed. Exclusion criteria were: residing in congregate settings (schools, prisons, homes) and temporary residents (less than 2 weeks in household of selected villages).

Asthma diagnosis

Sampled participants were interviewed by trained research assistants using a standardized questionnaire developed by adapting questions from internationally recognized questionnaires, including the World Health Organization (WHO) health survey^{1,22}, the international study of asthma and allergies in children (ISAAC)²² and the European community respiratory health survey (ECRHS) surveys²³. Asthma was defined as self-report of physician diagnosis, prescribed use of breathing medications for asthma or report of a wheeze in the last 12 months.

HIV diagnosis

HIV status in this survey was established by self-report. All participants were asked about their HIV status in private interviews. Responses were either HIV positive, HIV negative or unknown HIV status. HIV positive participants were classified as persons living with HIV (PLHIV).

Statistical analysis

Participants with unknown HIV status were excluded from this analysis. Participants' demographic and social characteristics and known asthma risk factors (tobacco smoking, allergy, family history of asthma, biomass use, and history of TB treatment) were summarized as proportions and compared between PLHIV and those who were not using Chi-square and Fisher's exact test statistics as appropriate.

We used Poisson regression with robust standard errors to estimate asthma prevalence and prevalence ratios (PR) between PLHIV and those who were not.²⁴ The Poisson model, an alternative for the log-binomial, was used due to convergence problems with the latter approach. The prevalence of asthma and the corresponding PRs among patients with key asthma risk factors namely tobacco smoking, biomass smoke exposure, family history of asthma, tuberculosis (TB) and allergy were also calculated. The PR ratio of asthma between PLHIV and those who were not living with HIV was then finally adjusted for these risk factors. Exposure to biomass smoke was defined as cooking in the living space (same room where participants slept), tobacco smoking was by self-report of being a smoker while allergy was considered to be present if a participant reported suffering in the past 12 months from any of the following: suffering in the past 12 months from any of watery itchy eyes, recurrent skin rash, or having sneezing, nasal congestion or rhinorrhea in the absence of an upper respiratory tract infection). To assess for the interaction between HIV and known asthma risk factors (tobacco smoking, biomass use, history of TB treatment, allergy, family history), we calculated age-dependent asthma prevalence comparing PLHIV and those who were not while keeping all other factors at zero and then by each factor. A graphical aid was used to visualize the age-dependent asthma prevalence by these factors.

6.3 RESULTS

Characteristics of study participants

Of 3416 UNAS participants, 2067 (60.5%) knew their HIV status and 103 reported to be living with HIV (5.0% of the group that knew their HIV status). The characteristics of these participants by HIV status are shown in Table 1. The proportions of participants with respiratory symptoms of cough, sputum production and wheezing did not differ by HIV status. However, the proportions with the symptom breathlessness differed significantly by HIV status, positive vs. negative (17.5% vs. 9.0%, $p=0.004$). Tobacco smoking was higher among PLHIV (12.6% vs. 7.9%, $p=0.086$) as well as having history of TB treatment (9.7% vs. 1.5%, $p<0.001$).

Table 1. Participant characteristics Please see my feedback in the previous file

	PLHIV (N=103)	Not PLHIV (N=1964)	P-value
Characteristic			
Male gender, n(%)	31 (30.1)	763 (38.8)	0.076
Age groups n(%)			<0.001
<15	1 (1.0)	91 (4.6)	
15-24	10 (9.7)	474 (24.1)	
25-34	27 (26.2)	510 (25.9)	
35-44	33 (32.0)	388 (19.7)	
45-54	27 (26.2)	304 (15.5)	
55-64	4 (3.9)	131 (6.7)	
65+	1 (1.0)	68 (3.5)	
Respiratory Symptoms n(%)			
Cough	23 (22.3)	404 (20.6)	0.665
Sputum	7 (6.8)	140 (7.1)	0.900
Wheezing	11 (10.7)	131 (6.7)	0.116
Shortness of breath	18 (17.5)	177 (9.0)	0.004
Risk factors and co-morbid conditions n (%)			
History of smoking	13 (12.6)	155 (7.9)	0.086
Exposure to bio-mass	24 (23.3)	385 (19.6)	0.357
Ever been treated for TB	10 (9.7)	30 (1.5)	<0.001
Allergy	42 (40.8)	721 (36.7)	0.400
Family history of asthma	15 (14.6)	220 (11.2)	0.295

PLHIV=people living with HIV, TB=tuberculosis

Prevalence of asthma by HIV status

The prevalence of asthma among PLHIV was 15.5% while that among those without HIV was 9.1%, PR 1.72 (95% CI: 1.07-2.75, $p=0.025$). After adjusting for gender, age, tobacco smoking, biomass exposure, TB treatment, family history of asthma and allergy, the PR ratio decreased to 1.54 (95% CI: 0.94-2.51, $p=0.085$), Table 2. A high prevalence of asthma among PLHIV was maintained at all ages irrespective of absence or presence of other risk factors of tobacco smoking, biomass use, allergy, family history of asthma and previous TB treatment (Figure 1). Considering only participants younger than 35 years the prevalence of asthma was still higher among PLHIV, PR 3.06 (Figure 2). The prevalence of asthma

among participants with known HIV status and unknown HIV status did not differ significantly (9.4% vs.9.0%, $p=0.689$), Table 3. HIV modified the association between asthma and other asthma risk factors, positive vs. negative: tobacco smoking (12% vs.8%, $p<0.001$) biomass use (11% vs. 7%, $p<0.001$), allergy (17% vs. 11%, $p<0.001$), family history asthma (17% vs. 11%, $p<0.001$) and TB treatment (15% vs. 10%, $p<0.001$), Figure 3.

Table 2. Asthma prevalence by HIV and potential confounding factors

	n (%)	Prevalence of asthma %	Crude PR (95% CI)	p	Adjusted PR [∞] (95% CI)	p-value
Characteristic						
HIV status						
Infected	103 (5.0)	15.5	1.72 (1.07-2.75)	0.025	1.54 (0.94-2.51)	0.085
Uninfected	1966 (95.0)	9.1	Reference		Reference	
Gender						
Female	1275 (61.6)	9.9	1.15 (0.87-1.53)	0.319	1.24 (0.92-1.68)	0.159
Male	794 (38.4)	8.6	Reference		Reference	
Smoking						
Yes	168 (8.1)	16.7	1.91 (1.32-2.76)	0.001	1.79 (1.23-2.60)	0.002
No	1901 (91.9)	8.7	Reference		Reference	
Biomass use						
Yes	409 (19.8)	14.2	1.74 (1.31-2.32)	<0.001	1.56 (1.18-2.07)	0.002
No	1659 (80.2)	8.1	Reference		Reference	
TB treatment						
Yes	40 (1.9)	22.5	2.46 (1.36-4.45)	0.003	2.20 (1.26-3.84)	0.005
No	2026 (98.1)	9.1	Reference		Reference	
Family history of asthma						
Yes	235 (11.4)	23.8	3.16 (2.39-4.18)	<0.001	2.41 (1.81-3.23)	<0.001
No	1832 (88.6)	7.5	Reference		Reference	
Allergy						
Yes	763 (36.9)	16.0	2.90 (2.20-3.83)	<0.001	2.45 (1.85-3.26)	<0.001
No	1306 (63.1)	5.5	Reference		Reference	
TB/HIV (HIV infected and history of TB treatment)						
Yes	10 (0.5)	10.0	1.07 (0.17-6.89)	0.946	0.20 (0.02-1.66)	0.135
No	2059 (99.5)	9.4	Reference		Reference	
Age in years ^φ			2.09 (1.52-2.88)	<0.001	1.83 (1.30-2.58)	0.001

^φ log transformed due to skewness, [∞] Adjusted for age, gender, smoking, biomass smoke exposure, allergy, history of TB and family history of asthma, CI=confidence interval, TB=tuberculosis, PR=prevalence ratio

Figure 1. Prevalence of asthma by age stratified by HIV status and other asthma risk factors: **a)** Prevalence of asthma by age and HIV status keeping all other factors at zero **b)** Prevalence of asthma by age and HIV status among participants exposed to biomass smoke **c)** Prevalence of asthma by age and HIV status among smokers **d)** Prevalence of asthma by age and HIV status among participants with history of allergy **e)** Prevalence of asthma by age and HIV status among participants with family history of asthma **f)** Prevalence of asthma by age and HIV status among participants with history of TB treatment

Figure 2. Asthma prevalence ratios (HIV+ vs HIV-) considering different ages of participants

Table 3. Participants characteristics by HIV status (known vs. unknown status)

	HIV status known (N=2069)	HIV status unknown (N=1347)	P-value
Characteristic			
Male gender	794 (38.4)	533 (39.6)	0.484
Age groups			<0.001
<15	92 (4.5)	280 (20.8)	
15-24	484 (23.4)	400 (29.7)	
25-34	537 (26.0)	144 (10.7)	
35-44	421 (20.4)	156 (11.6)	
45-54	331 (16.0)	144 (10.7)	
55-64	135 (6.5)	90 (6.7)	
65+	69 (3.3)	133 (9.9)	
Respiratory Symptoms			
Cough	427 (20.7)	284 (21.1)	0.751
Sputum	147 (7.1)	110 (8.2)	0.250
Wheezing	142 (6.9)	84 (6.2)	0.471
Shortness of breath	195 (9.4)	114 (8.5)	0.337
Risk factors and co-morbid conditions			
History of smoking	168 (8.1)	74 (5.5)	0.004
Exposure to bio-mass	409 (19.8)	289 (21.5)	0.235
Ever been treated for TB	40 (1.9)	10 (0.7)	0.005
Allergy	763 (36.9)	433 (32.2)	0.005
Family history of asthma	235 (11.4)	142 (10.6)	0.455
Asthma			
Positive	194 (9.4)	121 (9.0)	0.698

TB=tuberculosis

Figure 3. Asthma prevalence considering different known asthma risk factors (all p-values < 0.001)

Prevalence of asthma by other factors

Other factors associated with increased prevalence of asthma in this study were biomass use adjusted PR 1.56 (95% CI: 1.18-2.07, $p=0.002$), tobacco smoking 1.79 (95% CI: 1.23-2.60, $p=0.002$), history of TB treatment 2.20 (95% CI: 1.26-3.84, $p=0.005$), family history of asthma 2.41 (95% CI: 1.81-3.23, $p<0.001$), and allergy 2.45 (95% CI: 1.85-3.26, $p<0.001$), Table 2.

6.4 DISCUSSION

This study has established that the prevalence of asthma among PLHIV is higher than among those without HIV and that HIV modifies the associations of asthma with tobacco smoking, biomass use, TB, allergy and family history of asthma. The study also shows that the only respiratory symptom more prevalent in PLHIV than without PLHIV is breathlessness. In terms of asthma risk factors the study found that PLHIV have high rates of tobacco smoking and history of TB treatment.

A higher prevalence of asthma among PLHIV has been reported in previous studies in clinic-based studies in high income with low HIV prevalence.⁶⁻¹² In 248 HIV infected and 236 HIV uninfected males, the prevalence of wheezing was 54.4%, vs. 21.2%, $p<0.001$ ⁹ while in a study comparing 14,005 HIV infected patients with age matched HIV uninfected controls in Canada, the PR for asthma was 1.31 (95% CI 1.20-1.43) (12). In another study among 223 HIV patients in the USA, the prevalence of doctor diagnosed asthma was 20.6 compared to 8.2% in the general population.¹³ Although after adjusting for other risk factors of asthma such as smoking, biomass smoke, TB, allergy the PR ratio for asthma in PLHIV reduced to 1.54 with a trend p -value of 0.085. The results are however line with the findings from the studies above which increases the possibility that HIV is associated with asthma even in the present study

We investigated the effect HIV had on the risk of asthma from other asthma risk factors. We found that PLHIV had higher rates of smoking as previously reported.^{25, 26} The prevalence of asthma among tobacco smoking PLHIV was 12.6% compared to 7.9% of smokers who were not living with HIV. The finding of high smoking rates among PLHIV in this study has been reported in previous studies.^{25, 26} This finding therefore calls for heightened efforts to reduce smoking among PLHIV.”

We compared respiratory symptoms between HIV infected and HIV uninfected participants and found that there were no differences except for breathlessness. George *et al.* found that HIV infected persons had high rates of most respiratory symptoms.²¹ We cannot explain why we failed to observe these differences in respiratory symptoms apart from breathlessness. The excess breathlessness in the HIV infected participants might be due to interstitial and diffusion derangements that are so prevalent among HIV infected persons.²⁷⁻²⁹ Gingo *et al.* in a cross-sectional analysis of 158 HIV-infected individuals without acute respiratory symptoms or infection found that 55 (34.8%) participants had a significantly reduced DL_{CO} ($<60\%$ predicted).²⁹

This study had limitations most notably the use of self-report to determine HIV infection. Self-report as a means of determining HIV status has been reported to have low sensitivity but high specificity.^{30, 31} Among older adults (≥ 40 years) in South Africa, Rohr *et al* report a sensitivity of HIV self-report of 51.2% (95% CI: 48.2-54.3) and specificity was 99.0% (95% CI: 98.7-99.4).^{30, 31} The low sensitivity of self-report may also be present in our study, the self-reported prevalence of HIV in our survey is 3.1%,

which is much lower than the national prevalence of 6.2%.⁴ We believe that differential classification of HIV by asthma status is unlikely, but if present would likely tend to underestimate the prevalence ratio if patients without HIV are less likely to report HIV status. We performed further analysis on our data comparing demographic characteristics and asthma prevalence between participants with known HIV status and those with unknown HIV status, Table 4. As can be seen in this table the prevalence of asthma among these two groups did not significantly differ.

Another limitation of our study is that asthma was diagnosed based on history or current wheeze, prior physician diagnosis and being currently on asthma medications. However, the methods used in this study are the standard methods that are used in most asthma surveys including the ISAAC, ECRHS and the WHO health survey.^{1, 22, 23} We recognize that wheezing could be due to other diseases such as chronic obstructive pulmonary disease (COPD). Therefore, it is possible that some of the participants classified as asthma could have had COPD which is also known to be associated with HIV. We performed sensitivity analysis considering only participants who are younger than 35 years, the age below which the diagnosis of COPD is unlikely and found that the prevalence of asthma in age group was still higher among the HIV infected participants (Figure 1 left panel) implying that the association between asthma and HIV in this study might be a true one. There are however other conditions that can cause wheezing such as bronchiectasis, heart failure and mechanical airway obstruction^{32, 33} that we could not exclude although these conditions are deemed to be rare.

Despite the limitations, our findings have several scientific, healthcare and programmatic implications. Firstly, HIV care programs need to build capacity for diagnosis of asthma and its management. At the same time there may be need to test for HIV among asthma patients in high HIV burden settings and to know their ART status and the medications they are taking. Asthma and HIV co-morbidity can be associated with complexities that can arise while managing the two diseases notably drug-drug interactions and increased rates of adverse events as can occur with corticosteroids used in the management of asthma. Corticosteroids use in HIV infected persons has been associated with adverse outcomes such as the development of cancers like Kaposi's sarcoma and TB.³⁴⁻³⁶ Another key drug-drug interaction to consider is that between protease inhibitors and corticosteroids, which is mediated through the effects of PIs on the cytochrome CYP450 3A4 drug metabolism pathway.^{37, 38} This interaction can lead to complications such as Cushing's syndrome, hypertension and poor CD4 cell count recovery.³⁸ We found that HIV modified the risk of asthma from other risk factors. This calls for vigorous prevention of these risk factors among PLHIV. PLHIV in this study had higher rates of tobacco smoking. This calls for heightened efforts to reduce smoking among PLHIV since they may be more likely to develop tobacco associated lung diseases. In terms of science, our findings call for more research on the impact of HIV on asthma in high HIV burden settings and the mechanistic pathways of the HIV asthma interaction especially in settings with high rates of factors like TB and biomass smoke exposure. The impact of HIV on asthma prognosis also needs to be studied.

In conclusion, the prevalence of asthma among PLHIV in this survey is higher than among those without HIV. HIV also modifies the risk of asthma from other asthma risk factors such as tobacco smoking, TB, exposure to biomass, allergy and family history of asthma. PLHIV should be assessed for asthma and asthma patients should undergo HIV testing.

List of abbreviations

ART	Antiretroviral therapy
CD4	Cluster of differentiation 4
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CY	Cytochrome
ECRHS	European community respiratory health survey
HIV	Human immune deficiency virus
HHs	Households
IgE	Immunoglobulin E
IL-4	Interleukin-4
ISAAC	International study of asthma and allergies in children
LMICs	Low and middle-income countries
NCDs	Non-communicable diseases
PLHIV	People living with HIV
PR	Prevalence ratio
TB	Tuberculosis
UNAS	Uganda National asthma survey
USA	United States of America
WHO	World Health Organization

Declarations

Ethics approval and consent to participate: Ethics approval was obtained from the Mulago Hospital Research and Ethics committee and the Uganda National Council for Science and Technology. Participants provided written informed consent and were free to terminate study participation at any time during the study. For children between the ages of 12-18 years, we obtained their assent and parental/legal guardian consent.

Consent for publication

Not applicable, this manuscript does not contain any personal data.

Availability of data and material: The data of the Uganda National Survey is available with the authors.

Competing interests: All authors declare no conflict of interest relevant to this manuscript

Funding: This work was funded by the National Institutes of Health (NIH) (Award No. R24 TW008861) and NCS, UMCG, The Netherlands

Authors' contributions: Bruce Kirenga, Thys van der Molen, Moses Kamya and Corina de Jong conceived and designed the original survey, supervised data collection and interpreted the data. Bruce Kirenga and Lucian Davis conceived the idea of the current analysis of the survey data. Bruce Kirenga and Levicatus Mugenyi analyzed the data. Bruce Kirenga, and Wincelaus Katagira participated in and supervised data collection. All authors reviewed and contributed to the manuscript writing

Acknowledgements: The authors thank all study participants and research assistants as well as research managers who were involved in this study. Special thanks go to the data management team headed by Mr. Rogers Sekibira that ensured all data were entered, cleaned and available for analysis in a timely manner.

Authors' Information: Not applicable. No relevant author details available

References

1. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC public health*. 2012;12(1):204.
2. Marais BJ. Childhood tuberculosis: epidemiology and natural history of disease. *The Indian Journal of Pediatrics*. 2011;78(3):321-7.
3. Adeloye D, Chan KY, Rudan I, Campbell H. An estimate of asthma prevalence in Africa: a systematic analysis. *Croatian medical journal*. 2013;54(6):519-31.
4. Ayles H, Muyoyeta M, Du Toit E, Schaap A, Floyd S, Simwanga M, et al. Effect of household and community interventions on the burden of tuberculosis in southern Africa: the ZAMSTAR community-randomised trial. *The Lancet*. 2013;382(9899):1183-94.
5. Morgan BW, Siddharthan T, Grigsby MR, Pollard SL, Kalyesubula R, Wise RA, et al. Asthma and Allergic Disorders in Uganda: A Population-Based Study Across Urban and Rural Settings. *The Journal of Allergy and Clinical Immunology: In Practice*. 2018.
6. Puri A, Gingo M, Morris A. Asthma in HIV-infected population: a review of respiratory symptoms, pulmonary function abnormalities and pathophysiology. *Epidemiology: Open Access*. 2014;4(4).
7. Wallace JM, Stone GS, Browdy BL, Tashkin DP, Hopewell PC, Rosen MJ, et al. Nonspecific airway hyperresponsiveness in HIV disease. *Chest*. 1997;111(1):121-7.
8. O'Donnell CR, Bader MB, Zibrak JD, Jensen WA, Rose RM. Abnormal airway function in individuals with the acquired immunodeficiency syndrome. *Chest*. 1988;94(5):945-8.
9. Poirier CD, Inhaber N, Lalonde RG, Ernst P. Prevalence of bronchial hyperresponsiveness among HIV-infected men. *American journal of respiratory and critical care medicine*. 2001;164(4):542-5.
10. Crothers K, Huang L, Goulet JL, Goetz MB, Brown ST, Rodriguez-Barradas MC, et al. HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. *American journal of respiratory and critical care medicine*. 2011;183(3):388-95.
11. Lin RY, Lazarus TS. Asthma and related atopic disorders in outpatients attending an urban HIV clinic. *Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, & Immunology*. 1995;74(6):510-5.
12. Kendall CE, Wong J, Taljaard M, Glazier RH, Hogg W, Younger J, et al. A cross-sectional, population-based study measuring comorbidity among people living with HIV in Ontario. *BMC public health*. 2014;14(1):161.
13. Gingo MR, Wenzel SE, Steele C, Kessinger CJ, Lucht L, Lawther T, et al. Asthma diagnosis and airway bronchodilator response in HIV-infected patients. *Journal of allergy and clinical immunology*. 2012;129(3):708-14. e8.
14. Drummond MB, Kirk GD, Astemborski J, Marshall MM, Mehta SH, McDyer JF, et al. Association between obstructive lung disease and markers of HIV infection in a high-risk cohort. *Thorax*. 2011;thoraxjnl-2011-200702.
15. Wright DN, Nelson Jr RP, Ledford DK, Fernandez-Caldas E, Trudeau WL, Lockey RF. Serum IgE and human immunodeficiency virus (HIV) infection. *Journal of allergy and clinical immunology*. 1990;85(2):445-52.
16. Thuesen B, Husemoen L, Hersoug LG, Pisinger C, Linneberg A. Insulin resistance as a predictor of incident

- asthma-like symptoms in adults. *Clinical & Experimental Allergy*. 2009;39(5):700-7.
17. Drummond MB, Merlo CA, Astemborski J, Marshall MM, Kisalu A, Medyer JF, et al. The effect of HIV infection on longitudinal lung function decline among injection drug users: a prospective cohort. *AIDS (London, England)*. 2013;27(8):1303.
 18. Gingo MR, Morris A. Pathogenesis of HIV and the lung. *Current HIV/AIDS Reports*. 2013;10(1):42-50.
 19. Kidd P. Th1/Th2 balance: the hypothesis, its limitations, and implications for health and disease. *Alternative medicine review*. 2003;8(3):223-46.
 20. Deo SS, Mistry KJ, Kakade AM, Niphadkar PV. Role played by Th2 type cytokines in IgE mediated allergy and asthma. *Lung India: Official Organ of Indian Chest Society*. 2010;27(2):66.
 21. George MP, Kannass M, Huang L, Sciurba FC, Morris A. Respiratory symptoms and airway obstruction in HIV-infected subjects in the HAART era. *PloS one*. 2009;4(7):e6328.
 22. Asher M, Anderson H, Stewart A, Crane J, Ait-Khaled N, Anabwani G, et al. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *European Respiratory Journal*. 1998;12(2):315-35.
 23. Fitzpatrick C, Floyd K. A systematic review of the cost and cost effectiveness of treatment for multidrug-resistant tuberculosis. *Pharmacoeconomics*. 2012;30(1):63-80.
 24. Coutinho L, Scazufca M, Menezes PR. Methods for estimating prevalence ratios in cross-sectional studies. *Revista de saude publica*. 2008;42(6):992-8.
 25. Mdege ND, Shah S, Ayo-Yusuf OA, Hakim J, Siddiqi K. Tobacco use among people living with HIV: analysis of data from Demographic and Health Surveys from 28 low-income and middle-income countries. *The Lancet Global Health*. 2017;5(6):e578-e92.
 26. Mdodo R, Frazier EL, Dube SR, Mattson CL, Sutton MY, Brooks JT, et al. Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys. *Annals of internal medicine*. 2015;162(5):335-44.
 27. Doffman SR, Miller RF. Interstitial lung disease in HIV. *Clinics in chest medicine*. 2013;34(2):293-306.
 28. Semenzato G, Agostini C. HIV-related interstitial lung disease. *Current opinion in pulmonary medicine*. 1995;1(5):383-91.
 29. Gingo MR, He J, Wittman C, Fuhrman C, Leader JK, Kessinger C, et al. Contributors to diffusion impairment in HIV-infected persons. *European Respiratory Journal*. 2014;43(1):195-203.
 30. Rohr JK, Xavier Gómez-Olivé F, Rosenberg M, Manne-Goehler J, Geldsetzer P, Wagner RG, et al. Performance of self-reported HIV status in determining true HIV status among older adults in rural South Africa: a validation study. *Journal of the International AIDS Society*. 2017;20(1).
 31. VALIDITY OF DATA ON SELF-REPORTED HIV STATUS AND IMPLICATIONS FOR MEASUREMENT OF ARV COVERAGE IN MALAWI. [cited 2018 June 7]; Available from: <https://dhsprogram.com/pubs/pdf/WP81/WP81.pdf>.
 32. CLERF LH. DIFFERENTIAL DIAGNOSIS OF WHEEZING RESPIRATION. *Journal of the American Geriatrics Society*. 1953;1(9):623-6.
 33. Lillington GA, Lin H-w. Differential Diagnosis of Asthma in Adults Asthma, Occult Asthma, and Pseudoasthma. *Bronchial Asthma: Springer*; 1994. p. 171-87.

34. Lee C-H, Kim K, Hyun MK, Jang EJ, Lee NR, Yim J-J. Use of inhaled corticosteroids and the risk of tuberculosis. *Thorax*. 2013;68(12):1105-13.
35. Brassard P, Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and risk of tuberculosis in patients with respiratory diseases. *American journal of respiratory and critical care medicine*. 2011;183(5):675-8.
36. Gill PS, Loureiro C, Bernstein-Singer M, Rarick MU, Sattler F, Levine AM. Clinical effect of glucocorticoids on Kaposi sarcoma related to the acquired immunodeficiency syndrome (AIDS). *Annals of internal medicine*. 1989;110(11):937-40.
37. Foisy M, Yakiwchuk E, Chiu I, Singh A. Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. *HIV medicine*. 2008;9(6):389-96.
38. Saberi P, Phengrasamy T, Nguyen DP. Inhaled corticosteroid use in HIV-positive individuals taking protease inhibitors: a review of pharmacokinetics, case reports and clinical management. *HIV medicine*. 2013;14(9):519-29.

CHAPTER 7: The State of Ambient Air Quality in Two Ugandan Cities: A Pilot Cross-Sectional Spatial Assessment

Authors

Bruce J Kirenga^{1,†*}, Qingyu Meng^{2,†}, Frederik van Gemert³, Hellen Aanyu- Tukamuhebwa⁴, Niels Chavannes⁵, Achilles Katamba ⁶, Gerald Obai ⁷, Thys van der Molen³, Stephan Schwander^{2,†}, Vahid Mohsenin^{8†}

1. Division of Pulmonary Medicine, Department of Medicine, Makerere University College of Health Sciences, Kampala, Uganda; Email: brucekirenga@yahoo.co.uk
2. Department of Environmental and Occupational Health and Center for Global Public Health, School of Public Health, Rutgers University, NJ, USA; Emails: mengqi@sph.rutgers.edu; schwansk@sph.rutgers.edu
3. Department of General Practice, University of Groningen, University Medical Center Groningen, The Netherlands; Email: frgemert@xs4all.nl; t.van.der.molen@umcg.nl
4. Department of Paediatrics and Child Health, Makerere University College of Health Sciences, Kampala, Uganda; Email: hellen.aanyut@gmail.com
5. Department of Public Health and Primary Care, Leiden University Medical Center, The Netherlands; Email: n.h.chavannes@lumc.nl
6. Clinical Epidemiology and Biostatistics Unit, Department of Medicine, Makerere University College of Health Sciences, Kampala, Uganda; Email: akatamba@yahoo.com
7. Department of Physiology, Faculty of Medicine, Gulu University, Gulu, Uganda; Email: lekobai@gmail.com
8. Department of Medicine, Yale University School of Medicine, New Haven, CT, USA; Email: vahid.mohsenin@yale.edu

† Drs. Bruce Kirenga and Qingyu Meng are equally contributing co-first authors and Drs. Stephan Schwander and Vahid Mohsenin are co-senior authors

*Author to whom correspondence should be addressed; E-Mail: brucekirenga@yahoo.co.uk, Telephone: **+256782404431**

Published in Int. J. Environ. Res. Public Health 2015, 12, 8075-8091;

ABSTRACT

Air pollution is one of the leading global public health risks but its magnitude in many developing countries' cities is not known. We aimed to measure the concentration of particulate matter with aerodynamic diameter $<2.5\ \mu\text{m}$ ($\text{PM}_{2.5}$), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3) pollutants in two Ugandan cities (Kampala and Jinja). $\text{PM}_{2.5}$, O_3 , temperature and humidity were measured with real-time monitors, while NO_2 and SO_2 were measured with diffusion tubes. We found that the mean concentrations of the air pollutants $\text{PM}_{2.5}$, NO_2 , SO_2 and O_3 were $132.1\ \mu\text{g}/\text{m}^3$, $24.9\ \mu\text{g}/\text{m}^3$, $3.7\ \mu\text{g}/\text{m}^3$ and $11.4\ \mu\text{g}/\text{m}^3$, respectively. The mean $\text{PM}_{2.5}$ concentration is 5.3 times the World Health Organization (WHO) cut-off limits while the NO_2 , SO_2 and O_3 concentrations are below WHO cut-off limits. $\text{PM}_{2.5}$ levels were higher in Kampala than in Jinja ($138.6\ \mu\text{g}/\text{m}^3$ vs. $99.3\ \mu\text{g}/\text{m}^3$) and at industrial than residential sites ($152.6\ \mu\text{g}/\text{m}^3$ vs. $120.5\ \mu\text{g}/\text{m}^3$) but residential sites with unpaved roads also had high $\text{PM}_{2.5}$ concentrations ($152.6\ \mu\text{g}/\text{m}^3$). In conclusion, air pollutant concentrations in Kampala and Jinja in Uganda are dangerously high. Long-term studies are needed to characterize air pollution levels during all seasons, to assess related public health impacts, and explore mitigation approaches.

Keywords: ambient air pollution, particulate matter, nitrogen dioxide, sulfur dioxide, ozone, Uganda, Kampala, Jinja

7.1 INTRODUCTION

On the 25 March 2014, the World Health Organization (WHO) released new estimates of the contribution of air pollution to global mortality showing that seven million deaths were attributable to air pollution worldwide in the year 2012 (3.7 million due to ambient air pollution (AAP) and 4.3 million due to indoor air pollution (IAP)).¹ This number represents a doubling from the air pollution mortality rates estimated by WHO in the year 2004.^{1,2}

Air pollution is thus one of the leading global public health risks. Health problems commonly associated with air pollution exposure include: respiratory diseases (e.g., chronic obstructive pulmonary disease, asthma, lung cancer and acute respiratory infections in children) and cardiovascular diseases (such as ischemic heart disease and stroke).² Adverse health effects associated with air pollution exposure are particularly severe among vulnerable populations (e.g., people with respiratory diseases like asthma), older people, and children. Available data also show that air pollution has the potential to impair lung growth as a result of perinatal exposures thus threatening the health of entire generations.^{3,4,5,6} Although over 3000 substances are known to potentially contaminate air,⁷ the WHO has identified particulate matter (PM), nitrogen dioxide (NO₂), carbon monoxide (CO), sulfur dioxide (SO₂) and ozone (O₃) as the pollutants with greatest public health importance.² The United States (US) National Ambient Air Quality Standard (NAAQS) [8] designates all of the above plus airborne lead (Pb) as criteria pollutants.

WHO and the US Environmental Protection Agency (USEPA) have defined guideline limits for these pollutants that should not be exceeded in order to maintain and protect public health.^{9,10} The WHO limits for PM_{2.5}, PM₁₀, NO₂, SO₂, and O₃ are 25 µg/m³ (24-hour mean), 50 µg/m³ (24-hour mean), 200 µg/m³ (one-hour mean), 20 µg/m³ (24-hour mean), and 100 µg/m³ (eight-hour mean), respectively,⁹ while the limits for the same pollutants set by the USEPA are PM_{2.5} 35 µg/m³ (24-hour mean), PM₁₀ 150 µg/m³ (24-hour mean), NO₂ 100 ppb or 200 µg/m³ (one-hour mean), SO₂ 75 ppb or 150 µg/m³ (one-hour mean) and O₃ 0.075 ppm or 150 µg/m³ (one-hour mean).¹⁰

Data on the magnitude of air pollution in African cities is limited, particularly as it relates to Sub-Saharan Africa.¹¹ The WHO database provides an average PM_{2.5} value for Africa of 78 µg/m³ annual mean (which is almost three times the set limit).¹² A detailed review of the database shows that 18 African studies, seven of which were from South Africa, were used in generating this average, indicating a dearth of data on air pollution for the African continent. In most of the African studies, PM concentrations exceed WHO limits.

Data from African cities on gas phase pollutants are even sparser.¹¹ Available reports, however, indicate that concentrations of gas phase pollutants are low.^{13,14,15,16,17,18,19,20,21,22} Carmichael *et al.*, in an extensive study in Africa, Asia and South America, found that concentrations of gas phase pollutants of SO₂, NO₂ and ammonia were generally lower in the tropical regions than non-tropical regions of the studied countries.²³

For Uganda, data on air pollution is nearly nonexistent. To date, there is only one publication available, from our group, showing a PM concentration of 100 µg/m³ from a single pilot study measured in one district of Kampala.²⁴ The 2010 Uganda State of the Environment Report acknowledges this lack of air pollution data for Uganda.²⁵ The current study expands on our previous air pollution assessment efforts²²

and provides novel data on ambient concentrations of four key air pollutants ($\text{PM}_{2.5}$, NO_2 , SO_2 , and O_3) at various sites in Kampala and Jinja.

7.2 METHODS

7.2.1 Study Design

This is a cross-sectional, spatial, pilot assessment of ambient air concentrations of $\text{PM}_{2.5}$, NO_2 , SO_2 , and O_3 at different sites in three different land use areas in Kampala and Jinja during the period from 30 June to 27 July, 2014.

7.2.2 Study Sites and Monitoring Approaches

Air pollutant monitoring was conducted in Kampala and Jinja. Kampala, the capital city of Uganda, covers an area of 197 km² and is spread over 22 hills at an altitude of 1120 m above sea level. The city's day and night population is 3 million and 1.72 million people, respectively.²⁶ The day population represents Kampala residents and commuters entering the city from outside regions for work, education and business. Annual rainfall in Kampala ranges from 1750–2000 mm with peak wet seasons from March to May and from September to November. The dry seasons are between June and July, and December and February. The average annual temperature is 21.9° C and relative humidity ranges from 53–89%.²⁷

Jinja is the second largest city in Uganda, located 80 km east of Kampala and covers a land area of 28 km² at an altitude of 1230 m above sea level. Jinja has a day population of 300,000 people and a night population of 89,700 people.²⁶ The annual rainfall averages 1125 mm.²⁸

Air pollutant sampling sites in both cities were selected to represent different topographies and land use areas: commercial, industrial, and residential. According to the land classification system of local climate zones (LCZ), all of the sampling sites belong to the following categories: open low-rise or sparsely built.²⁹ Representative photographs of these sites are shown in [Figure 1](#). Sites for PM monitoring were fewer than sites for gas phase pollutant monitoring, as equipment for PM sampling was limited.

Figure 1. Representative images of sampling sites. Sampling site: a) central monitoring site; b) paved residential; c) unpaved residential, low income; d) industrial area; e) unpaved residential high income; and f) commercial center.

Areas of the cities characterized by high commercial activities such as trading, small-scale manufacturing and high traffic were selected as commercial land use areas. Industrial land use areas were in designated industrial areas of the cities. In Kampala, the industries surrounding the monitoring sites were involved in textile, steel and food products, while in Jinja we observed food products, plastics and steel industries. Land use areas defined as residential were divided into two categories, those with paved/tarmac roads and those with unpaved/murram roads.

Meteorological parameters (temperature and humidity) and O_3 were monitored at one central commercial

site in Kampala city. Meteorological data (2012–2014) were also retrieved from National Weather Services to compare the year-round meteorological conditions and the meteorological conditions during sampling.

7.2.3 Air Pollutant Sampling Methods

PM_{2.5} concentrations were measured over periods of 24 hours from 30 June to 27 July 2014 with a real-time aerosol monitor, DUSTTRACK II-8530 (TSI Inc, Shoreview, MN) at 18 sites (15 in Kampala and 3 in Jinja) that can assess PM_{2.5} concentrations in a range from 1 µg/m³ to 400 mg/m³. Prior to all measurements, the DUSTTRACK monitor was calibrated using the federal reference method, and zero-calibrated prior to each sampling session. All data were saved on the monitor until the end of study when it was downloaded into an excel database for analysis in Stata 11.2.

Concentrations of NO₂ and SO₂ were measured with Combo diffusion tubes (NO₂ and SO₂, Ormantine, FL, USA) at 28 study sites (22 in Kampala and 6 in Jinja). At each study site, two duplicate diffusion tubes were secured on the outside walls of selected buildings, 3–5 meters above ground. Sampling sites were selected to reflect different land use patterns and geographic topography, and each building was at least 3 meters away from immediate emission sources. The sampling height was selected for the safety of the passive samplers and was within the USEPA ambient monitoring siting criteria (*i.e.*, < 15 m). Each passive diffusion tube was exposed to ambient air for two weeks. Sampling starting and sampling end times were recorded. Two traveling blanks were included for each city. Prior to, and following, sampling periods, the samplers were stored at 4 °C. Combo diffusion tubes were shipped to Gradkos laboratory in England where NO₂ and SO₂ analyses were conducted on a Dionex ICS1100 ICU10 ion chromatography system (Thermo Fisher Scientific Inc., Waltham, MA, USA). O₃ was measured with a federal equivalent real-time monitor (POM, 2B Technologies, CO, USA) that was calibrated before the study period, and cleaned daily during the sampling period.

7.2.4 Meteorological Measurements

Temperature and humidity were monitored daily for the first seven days of the study period with a real-time monitor (HOBO U23, OnSet, MA, USA). The monitor was calibrated prior to sampling, and cleaned daily during the sampling period.

7.2.5 Data Analysis

Data from all monitors were downloaded directly into a Microsoft Excel database and analyzed using Stata 11.2 (StataCorp LP, College Station, TX). Descriptive statistics were used to summarize all pollutant concentrations and meteorological data. Mean pollutant concentrations were compared between land use areas and cities by t-tests. A *p*-value of <0.05 was considered statistically significant. Concentrations of travelling blanks (*i.e.*, tubes not exposed to sampling environments) were subtracted from all measured SO₂ and NO₂ concentrations prior to statistical analysis.

7.2.6 Ethics Approval

The study protocol was approved by the Mulago Hospital Research and Ethics Committee and the Uganda National Council for Science and Technology.

7.3 RESULTS

7.3.1 Temperature and Humidity

Temperature and relative humidity were measured at the central monitoring location during the first week (30 June to 5 July, 2014) of sampling. The mean ($\pm$ standard deviation (SD)) ambient temperature was 24.7 ± 1.9 °C (maximum 26.4 °C, minimum 21.1 °C). Mean humidity was $63.5\% \pm 5.7$ (maximum 74.4%, minimum 58.0%). We did not monitor temperature and humidity data further due to limited equipment availability. Archived temperature and humidity data from the National Weather Services (at Entebbe Airport) was used instead and is presented in [Table 1](#) showing largely constant weather conditions during the entire air pollution monitoring period.

Table 1. Meteorological conditions during sampling days

Sampling Date	Minimum Temperature, °C	Maximum Temperature, °C	Average Temperature, °C	Average Relative Humidity, %	Wind Speed, Km/h	Precipitation, mm
June 30	19	26	22	80	8	0.0
July 1	18	26	22	77	8	0.0
July 2	18	26	22	77	8	0.0
July 3	19	26	22	80	10	0.0
July 4	19	26	22	76	7	0.0
July 5	17	26	22	76	9	0.0
July 6	19	26	22	70	9	0.0
July 7	18	25	22	81	11	0.0
July 8	18	25	22	75	11	0.0
July 9	19	20	20	96	4	0.0
July 10	18	23	--*	--	--	--
July 11	17	24	20	76	11	0.0
July 12	20	23	22	84	10	0.0
July 13	19	25	22	76	9	0.0

*Data were missing

** The historical minimum and maximum temperatures during the dry season are 18 and 28 °C for January, 18 and 28 °C for February, 17 and 25 °C for June, 17 and 25 °C for July, 16 and 25 °C for August, 17 and 27 °C for December

7.3.2 PM_{2.5}

PM_{2.5} concentrations were measured at 18 sites for an average sampling period of 21 hours and 15 minutes (maximum 24 hours, minimum 7 hours). Spatial variations of PM_{2.5} pollution levels in Kampala are shown in Figure 2a.

Figure 2. The spatial variation of $PM_{2.5}$ (a) and NO_2 (b) in Kampala.

The $PM_{2.5}$ concentrations by sampling site are presented in a [supplementary Table S1](#). The mean 24-hour $PM_{2.5}$ concentrations calculated for all study sites was $132.1 \mu\text{g}/\text{m}^3$. The concentration measured by the real-time monitor was comparable to the filter-based approach. At the central monitoring site (city center), the $PM_{2.5}$ mass concentrations were $90.4 \mu\text{g}/\text{m}^3$ obtained from the filter-based approach vs. $94.0 \mu\text{g}/\text{m}^3$ obtained from the real-time monitor. By city, 24-hour mean $PM_{2.5}$ concentrations in Kampala were higher than in Jinja, but the difference did not reach statistical significance ($138.6 \mu\text{g}/\text{m}^3$ and $99.3 \mu\text{g}/\text{m}^3$, $p = 0.20$). By land use, $PM_{2.5}$ and nitrogen dioxide pollution levels are shown in [Table 2](#). The highest 24-hour mean $PM_{2.5}$ concentrations were observed at the industrial ($156 \mu\text{g}/\text{m}^3$) followed by residential areas with unpaved roads ($152.6 \mu\text{g}/\text{m}^3$) and commercial land use areas ($129.4 \mu\text{g}/\text{m}^3$). Residential and office areas with paved roads had the lowest mean PM concentrations ($88.3 \mu\text{g}/\text{m}^3$). Compared to residential areas with paved roads, residential areas with unpaved roads had significantly higher mean 24-hour $PM_{2.5}$ concentrations ($152.6 \mu\text{g}/\text{m}^3$ vs. $88.3 \mu\text{g}/\text{m}^3$, $p = 0.045$). Considering both industrial and commercial areas as nonresidential, no significant differences were noted between nonresidential and residential areas ($131.0 \mu\text{g}/\text{m}^3$ vs. $132.8 \mu\text{g}/\text{m}^3$, $p = 0.93$). The 24-hour mean $PM_{2.5}$ concentration at a site in Jinja with unpaved roads was comparable to sites with unpaved roads in Kampala ($161 \mu\text{g}/\text{m}^3$ vs. $151.4 \mu\text{g}/\text{m}^3$). The mean $PM_{2.5}$ concentration at sites with paved roads in Jinja, however, was lower than that at similar sites in Kampala ($68.5 \mu\text{g}/\text{m}^3$ vs. $108.0 \mu\text{g}/\text{m}^3$).

Table 2. PM_{2.5} and NO₂ concentration by land use

Land use category	PM _{2.5}			NO ₂	
	Mean (SD) 24-hour average	Mean (SD) minimum	Mean (SD) Maximum	Mean (SD) NO ₂ (µg/m ³)	Mean (SD) NO ₂ (ppb)
Commercial area	129.4(38)	4.82(31)	284.4(89)	32.19(12.19)	16.79(6.49)
Industrial area	156(0)	8.2(0)	384(0)	22.69(5.76)	11.76(2.99)
Residential unpaved (murrum) road	152.6(44)	23.1(35)	346.1(95)	20.09(5.67)	11.61(4.88)
Residential/office paved (tarmac)	88.3(50)	3.9(27)	155(66)	18.39(4.39)	11.43(3.16)

7.3.4 Gas Phase Pollutants

Duplicate diffusion tubes were used for sampling SO₂ and NO₂ at each monitoring site. Each tube can simultaneously collect NO₂ and SO₂. The concentrations of NO₂ and SO₂ at each monitoring site were calculated as the average of the readings of the two tubes.

NO₂ and SO₂ concentrations were measured at a total of 28 monitoring sites (22 in Kampala and six in Jinja). In Kampala, one of the SO₂ duplicate tubes could not be retrieved at two monitoring sites. In Jinja, both NO₂ tubes could not be retrieved at one site and one SO₂ tube only was retrieved at one site. Therefore, 27 NO₂ and SO₂ sampling tubes were available for analysis (22 from Kampala and five from Jinja). The mean monitor exposure time was 330.34 (±25.54) hours or 13 days and 19 hours. The overall precision, expressed as coefficient of variation based on 22 pairs of co located sampling, was 14.0%.

7.3.5 Nitrogen Dioxide

NO₂ concentrations determined at the different sampling sites are shown in [supplementary Table S2](#). The mean two-week NO₂ concentration was 24.9 µg/m³.

By city, Kampala air was characterized by a higher mean total NO₂ concentration than that of Jinja (26.69 µg/m³ vs. 17.49 µg/m³, $p = 0.07$). The spatial variations of NO₂ concentration levels in Kampala are shown in [Figure 2b](#).

NO₂ concentrations by land use are shown in [Table 2](#). The highest NO₂ concentrations were observed in commercial land use areas (32.19 µg/m³) and the lowest in residential land use areas with paved roads (18.39 µg/m³). The mean NO₂ concentrations in commercial (including industrial) land use areas were significantly higher than in residential land use areas (32.19 µg/m³ vs. 19.69 µg/m³, $p = 0.002$). NO₂ concentrations measured in residential land use areas did not significantly differ from those in industrial land use areas (19.69 µg/m³ vs. 22.69 µg/m³, $p = 0.46$). Similarly, NO₂ concentrations in commercial land use areas did not significantly differ from those in industrial land use areas (32.19 µg/m³ vs. 22.69 µg/m³, $p = 0.22$).

7.3.6 Sulfur Dioxide

SO₂ was measured at all study sites and in all land use areas where NO₂ was measured. Levels of detectable SO₂ concentrations are shown in [supplementary Table S3](#). SO₂ concentrations were below

detection limit ($<0.03 \mu\text{g}/\text{m}^3$) at 20 of the 27 monitoring sites. The two-week mean SO_2 concentration at all monitoring sites was $3.79 \pm 3.0 \mu\text{g}/\text{m}^3$.

By city, there was only one monitoring site in Jinja where SO_2 concentrations reached detectable levels. This site, in an industrial land use area of Jinja, had a higher SO_2 concentration level ($7.3 \mu\text{g}/\text{m}^3$) than that in the industrial land use area of Kampala ($<0.69 \mu\text{g}/\text{m}^3$). Six other monitoring sites in Kampala also showed SO_2 concentrations above detection limit (mean $3.11 \mu\text{g}/\text{m}^3$). Comparing SO_2 concentrations by land use, concentrations were highest in industrial land use areas ($7.39 \mu\text{g}/\text{m}^3$), followed by commercial land use areas ($3.69 \mu\text{g}/\text{m}^3$), then residential land use areas with paved roads ($2.79 \mu\text{g}/\text{m}^3$), or unpaved roads ($2.39 \mu\text{g}/\text{m}^3$).

7.3.7. Ozone

The mean one-hour O_3 concentration at the monitoring site established at Lourdel Road, Wandegeya in Kampala measured over a period of seven days was $11.4 \mu\text{g}/\text{m}^3$ ($\pm 4.8 \mu\text{g}/\text{m}^3$). O_3 concentrations varied considerably across the sampling period (Figure 3).

Figure 3. Distribution of O_3 concentrations (1-min average) measured at the central monitoring site in Kampala.

7.4 DISCUSSION

This pilot study demonstrates presence of high PM concentrations and low gas phase air pollutant levels in Kampala and Jinja between 30 June and 17 July, 2014. The observed mean $\text{PM}_{2.5}$ concentration of $132.1 \mu\text{g}/\text{m}^3$ (5.3-fold above the limit defined by WHO) across all monitoring sites in the current study is comparable with the mean $\text{PM}_{2.5}$ concentration of $104.9 \mu\text{g}/\text{m}^3$ described in an earlier single-site pilot study from a district in Kampala.²⁴ As expected, particulate air pollution levels were found to be greatest in areas with high commercial/industrial land use and unpaved roads.

The observed mean PM_{2.5} concentration of 132.1 µg/m³ in the current study clearly exceeds the mean PM concentration of 78 µg/m³ calculated for the African region and reported in the WHO 2014 publication of the global state of air quality from 1600 cities in 91 countries.¹² Within the East African region, however, the mean PM concentration (132.1 µg/m³) observed in the current study is comparable with that reported from Nairobi/Kenya (128.7 µg/m³) and significantly higher than that reported from Dar es Salaam/Tanzania (26 µg/m³).^{17,30}

Sources of particulate air pollution described in the studies of African cities are typically emissions from vehicles, re-suspended dust from unpaved roads, smoke from indoor biomass fuel use and garbage burning, and industrial sites.^{14,31,32} During the current study, we observed source emissions of dust and soil blown by wind from unpaved roads, black smoke exhausts from cars, trucks and busses and smoke from burning household garbage in both Kampala and Jinja. High PM levels in residential land use areas with unpaved roads without industrial activity or high traffic volume, suggest that re-suspended dust significantly contributes to high PM levels. High PM levels in commercial land use areas with high traffic volume and paved roads, in contrast, suggest that vehicle emissions represent another significant source of PM in Kampala and Jinja. Dust from unpaved roads in the suburbs of both cities appears to be carried by human activities into areas with paved roads.

Ambient air PM composition has been reported in some African cities.^{16,24,33} Our earlier pilot study in Kampala found that more than 90% of PM_{2.5} studied at a sampling site in the Mpererwe district of Kampala was comprised of crustal species (probably re-suspended soil dust) and carbonaceous aerosol.²⁴ In Dar es Salaam, a study of PM collected close to a vehicle traffic site found carbon to be the main component suggesting vehicular emissions as its main source.³³ In Nairobi, Gaita *et al.* found that vehicle traffic, mineral dust, industrial activity, combustion and a mixed factor (composed of biomass burning, secondary aerosol and aged sea salt) were the main sources of PM air pollution.³² Mineral dust and traffic were responsible for approximately 74% of PM_{2.5} mass.³² Based on our findings and observations in the current pilot study we speculate that re-suspended dust and vehicular emissions are the primary sources of PM_{2.5} in Kampala and Jinja and may also be significant contributors to air pollution in other African cities.

We also assessed the concentration of three key gas phase pollutants (NO₂, SO₂ and O₃) in Kampala and Jinja. Even though concentrations of NO₂, SO₂ and O₃ were below WHO guideline levels (200 µg/m³ one-hour mean, 20 µg/m³ 24-hour mean and 100 µg/m³ eight-hour mean, respectively²) we recognize that our findings cannot be directly compared with WHO air quality standards due to differences in averaging times. However, our findings are comparable with findings from other gas phase pollutant studies in Africa.^{13,14,15,17} We do not know why gas phase pollutants in our study and other studies from Africa are low. Climatic conditions in the studied areas may facilitate adsorption of gas phase pollutants onto PM. As PM concentrations were found to be high in the current study and other studies in Africa this may explain the observed low concentrations of gas phase pollutants.

Conclusions from the current cross-sectional study have to be made considering that temporal variations of air pollutant concentrations could not be assessed, which is a major limitation of this pilot study, especially for PM_{2.5}. Due to the limitation of the number of real-time instruments (*i.e.*, only one DustTrack), we could not measure PM_{2.5} concentrations at multiple sites at the same time. Therefore, we

were unable to differentiate spatial variation from temporal variation in PM_{2.5} concentrations. However, the meteorological data in [Table 1](#) suggests that the weather conditions during our measurements were quite consistent, minimizing the possibility of the impact of weather on PM_{2.5} concentrations. Given that this study was conducted within a short period of time, source emission profiles in different locations will not be expected to change dramatically. Therefore, the measured PM_{2.5} spatial variation at minimum suggests the heterogeneous pattern of PM_{2.5} in Kampala.

In addition, PM_{2.5} concentrations (132.1 µg/m³) observed in this study (dry season) are consistent with findings from our earlier study, in which PM_{2.5} (104.3 µg/m³) was collected in December 2013 (also a dry season). Meteorological conditions during this pilot study were typical in Kampala for dry seasons, as shown in [Table 1](#). We are aware of the impact of weather and seasonal variations on air pollutant concentrations and expect PM_{2.5} concentrations to be different in rainy seasons. Future studies will have to expand air pollution monitoring to other cities and parts of Uganda, cover all weather seasons and begin exploring air pollution effects on public health, in particular lung health in urban populations of Uganda.

7.5 CONCLUSIONS

This study suggests that high level PM air pollution is prevalent in urban and suburban areas in Uganda, with PM_{2.5} concentrations above 100 µg/m³ in multiple locations in Kampala. Land use characteristics define ambient PM_{2.5}, NO₂ and SO₂ concentrations. Long-term exposures to the observed high levels of air pollution likely represent a major risk to public health in Kampala and Jinja. Long-term studies are needed to assess air pollution levels during the course of multiple weather seasons and the health impact in exposed populations.

Acknowledgements

The authors wish to thank Yale University office of Global Health, International Primary Care Respiratory Group, Center for Global Public Health at Rutgers School of Public Health, Rutgers Centers for Global Advancement and International Affairs (GAIA Centers), NIEHS R01ES020382-02 (S. Schwander), American Lung Association SB230016N (for Q Meng), and PES005022 for funding the study. We also thank Prof. Asghar Rastegar from the Yale University School of Medicine for his guidance during the design and implementation of this project. Special thanks go to Ms. Laura Crawford from the Yale University office of Global Health for her exemplary organization of the study equipment and logistics and to the research assistants (Stephen Kyaligonza and Simon Onanyang) for their dedicated efforts during data collection. We thank Dr. Denis Bwayo and Mr. Ahmed Mawa for their assistance with identification of the sampling sites in Jinja.

Author Contributions

Bruce Kirenga, Qingyu Meng, Stephan Schwander and Vahid Mohsenin conceived the study, Bruce Kirenga, Meng Qingyu, Stephan Schwander and Vahid Mohsenin designed the experiments; Bruce Kirenga, Meng Qingyu, Gerald Obai and Hellen Aanyu performed the experiments; Bruce Kirenga, Meng Qingyu, Achilles Katamba analyzed the data; Bruce Kirenga, Meng Qingyu, Stephan Schwander, Vahid Mohsenin, Thys van der Molen and Frederik van Gemert contributed reagents/materials/analysis tools; all authors participated in the writing of the paper.

Conflicts of Interest: None

7.6 REFERENCES and NOTES

1. 7 million premature deaths annually linked to air pollution. [cited 2014 August 22]; Available from: <http://www.who.int/mediacentre/news/releases/2014/air-pollution/en/>
2. World Health Organisation. Health topics. Air pollution. [cited 2014 May 1]; Available from: http://www.who.int/topics/air_pollution/en/
3. Body Burden – The pollution in newborns. A benchmark investigation of industrial chemicals, pollutants and pesticides in umbilical cord blood. Environmental Working Group, July 14, 2005. [cited; Available from: <http://www.ewg.org/research/body-burden-pollution-newborns>
4. Salvi S. Health effects of ambient air pollution in children. *Paediatr Respir Rev*. 2007; **8**(4): 275-80.
5. Kajekar R. Environmental factors and developmental outcomes in the lung. *Pharmacol Ther*. 2007; **114**(2): 129-45.
6. Fleischer NL, Merialdi M, van Donkelaar A, Vadillo-Ortega F, Martin RV, Betran AP, et al. Outdoor air pollution, preterm birth, and low birth weight: analysis of the world health organization global survey on maternal and perinatal health. *Environmental health perspectives*. 2014; **122**(4): 425.
7. Fenger J. Urban air quality. *Atmospheric Environment*. 1999; **33**(29): 4877-900.
8. Clean Air Act [cited 2014 August 22]; Available from: <http://www.epw.senate.gov/envlaws/cleanair.pdf>
9. Organization WH. WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide: global update 2005: summary of risk assessment. 2006.
10. National Ambient Air Quality Standards (NAAQS). [cited 2014 August 2014]; Available from: <http://www.epa.gov/air/criteria.html>
11. Petkova EP, Jack DW, Volavka-Close NH, Kinney PL. Particulate matter pollution in African cities. *Air Quality, Atmosphere & Health*. 2013; **6**(3): 603-14.
12. Ambient (outdoor) air pollution in cities database 2014. [cited 2014 August 22]; Available from: http://www.who.int/phe/health_topics/outdoorair/databases/cities/en/
13. Khoder MI. Diurnal, seasonal and weekdays-weekends variations of ground level ozone concentrations in an urban area in greater Cairo. *Environmental monitoring and assessment*. 2009; **149**(1-4): 349-62.
14. Arku RE, Vallarino J, Dionisio KL, Willis R, Choi H, Wilson JG, et al. Characterizing air pollution in two low-income neighborhoods in Accra, Ghana. *Sci Total Environ*. 2008; **402**(2-3): 217-31.
15. Moodley KG, Singh S, Govender S. Passive monitoring of nitrogen dioxide in urban air: a case study of Durban metropolis, South Africa. *J Environ Manage*. 2011; **92**(9): 2145-50.
16. Etyemezian V, Tesfaye M, Yimer A, Chow J, Mesfin D, Nega T, et al. Results from a pilot-scale air quality study in Addis Ababa, Ethiopia. *Atmospheric Environment*. 2005; **39**(40): 7849-60.
17. Jackson MM. Roadside concentration of gaseous and particulate matter pollutants and risk assessment in Dar-es-Salaam, Tanzania. *Environ Monit Assess*. 2005; **104**(1-3): 385-407.
18. Lindén J. Intra-urban air pollution in a rapidly growing Sahelian city. *Environment international*. 2012; **40**: 51-62.
19. Josipovic M, Annegarn HJ, Kneen MA, Pienaar JJ, Piketh SJ. Concentrations, distributions and critical level exceedance assessment of SO₂, NO₂ and O₃ in South Africa. *Environmental monitoring and*

- assessment. 2010; **171**(1-4): 181-96.
20. Kilabuko JH, Matsuki H, Nakai S. Air quality and acute respiratory illness in biomass fuel using homes in Bagamoyo, Tanzania. *Int J Environ Res Public Health*. 2007; **4**(1): 39-44.
 21. El-Dars FMS. Monitoring ambient sulfur dioxide levels at some residential environments in the Greater Cairo urban Region--Egypt. *Environmental monitoring and assessment*. 2004; **95**(1-3): 269-86.
 22. Adon M, Galy-Lacaux C, Yoboué V, Delon C, Lacaux J, Castera P, et al. Long term measurements of sulfur dioxide, nitrogen dioxide, ammonia, nitric acid and ozone in Africa using passive samplers. *Atmospheric Chemistry and Physics*. 2010; **10**(15): 7467-87.
 23. Carmichael GR, Fern M, Thongboonchoo N, Woo J-H, Chan L, Murano K, et al. Measurements of sulfur dioxide, ozone and ammonia concentrations in Asia, Africa, and South America using passive samplers. *Atmospheric Environment*. 2003; **37**(9): 1293-308.
 24. Schwander S, Okello CD, Freers J, Chow JC, Watson JG, Corry M, et al. Ambient particulate matter air pollution in Mpererwe District, Kampala, Uganda: a pilot study. *J Environ Public Health*. 2014; **763934**(10): 17.
 25. State Of The Environment Report For Uganda 2010. [cited 2014 August 22]; Available from: <http://library.health.go.ug/publications/service-delivery-public-health/environment-and-sanitation/state-environment-report>
 26. Uganda Statistical Abstract 2012. [cited 2014 August 22]; Available from: <http://www.ubos.org/onlinefiles/uploads/ubos/pdf%20documents/2012StatisticalAbstract.pdf>
 27. District profile. [cited 2014 August 22]; Available from: http://ww2.unhabitat.org/programmes/ump/documents/kampala_cds.doc
 28. Jinja Municipality profile. [cited 2014 August 22]; Available from: <http://www.skelleftea.se/Skol%20och%20kulturkontoret/Innehallssidor/Bifogat/JINJA%20MUNICIPALITY%20PROFILE.pdf>
 29. Stewart ID, Oke TR. Local climate zones for urban temperature studies. *Bulletin of the American Meteorological Society*. 2012; **93**(12): 1879-900.
 30. Kinney PL. Traffic Impacts on PM(2.5) Air Quality in Nairobi, Kenya. *Environmental science & policy*. 2011; **14**(4): 369-78.
 31. Ofosu FG, Hopke PK, Aboh IJ, Bamford SA. Biomass burning contribution to ambient air particulate levels at Navrongo in the Savannah zone of Ghana. *J Air Waste Manag Assoc*. 2013; **63**(9): 1036-45.
 32. Gaita S, Boman J, Gatari M, Pettersson J, Janhäll S. Source apportionment and seasonal variation of PM 2.5 in a Sub-Saharan African city: Nairobi, Kenya. *Atmospheric Chemistry and Physics*. 2014; **14**(18): 9977-91.
 33. Mkoma SL, Chi X, Maenhaut W. Characteristics of carbonaceous aerosols in ambient PM10 and PM_{2.5} particles in Dar es Salaam, Tanzania. *Sci Total Environ*. 2010; **408**(6): 1308-1

7.7 Supplementary Tables

Table S1. PM_{2.5} concentrations at different sites in Kampala and Jinja

Site	City	Land use	Test Length (hr: mins)	PM _{2.5} concentration, µg/m ³			Time minimum (hr:mins:sec)	Time maximum (hr:mins:sec)
				24 hour average	Minimum	Maximum		
Bugolobi	Kampala	Residential/office paved (tarmac) road	24:00	163	66	254	16:18	23:18:48
Kampala Industrial area	Kampala	Industrial area	23:35	156	82	384	16:04:46	23:04:46
Kisimira road	Jinja	Residential/office paved (tarmac) road	24:00	68	39	119	6:02:42	21:02:42
Rippon garden Nile avenue	Jinja	Residential/office paved (tarmac) road	24:00	69	50	124	16:04:15	8:04:15
School village Tenywa road Walukuba East	Jinja	Residential unpaved (murrum) road	18:46	161	0	285	11:45:21	18:45:21
Kabowa Gabunga road	Kampala	Residential unpaved (murrum) road	24:00	156	40	362	14:45:47	7:45:47
Kamwokya, Kyebando road	Kampala	Commercial area	24:00	88	0	217	13:05:53	14:05:53
Katanga, Wandegeya	Kampala	Commercial area	24:00	108	52	248	6:56:31	18:56:31
Kawala Bwaise road	Kampala	Residential unpaved (murrum) road	23:35	135	0	291	13:54:31	21:54:31
Kiwatule Central 1	Kampala	Residential unpaved (murrum) road	7:00	114	90	22	17:43:30	20:43:30
Kololo Ekobo road	Kampala	Residential/office paved (tarmac) road	18:00	53	2	123	17:43:28	10:43:28
Kyanja Nazareth road	Kampala	Residential unpaved (murrum) road	24:00	100	55	317	11:15:43	21:15:43
Lungujja Busega Kibumbiro	Kampala	Residential unpaved (murrum) road	22:09	240	0	535	7:38:18	8:38:18
Mulago Mulago Hill road	Kampala	Commercial area	24:00	143	59	225	9:43:39	2:43:39
Amir street Nakasero	Kampala	Commercial area	19:00	187	85	434	16:14:20	2:14:20
Nalukolongo Kweba zone	Kampala	Residential unpaved (murrum) road	18:16	133	0	401	9:28:42	0:28:42
Nansana Naluvule	Kampala	Residential unpaved (murrum) road	22:32	182	0	358	14:26:25	23:26:25
Lourdell road, wandegeya	Kampala	Commercial area	17:00	121	45	298	21:57:34	1:57:34

Table S2. Concentration of ambient air nitrogen dioxide at different sites in Kampala and Jinja cities

Site	Land use	City	Exposure	NO ₂ _{total (ug)}	NO ₂ ug/m ³	NO ₂ ppb
Amir Street - Nakasero	Commercial centre	Kampala	309.55	1.15	49.90	26.96
Mutundwe - Kigaga Zone	Residential unpaved (murrum) road	Kampala	337.75	0.25	9.32	4.85
Nalukolongo - Kweba Zone	Residential unpaved (murrum) road	Kampala	337.67	0.67	26.22	13.64
Kawala - Bwaise Road	Residential unpaved (murrum) road	Kampala	339.50	0.62	24.33	12.66
Kiwatule Central I.	Residential unpaved (murrum) road	Kampala	336.00	0.56	22.08	11.48
Bwaise - Makerere - Kavule Road	Residential unpaved (murrum) road	Kampala	308.43	0.54	23.33	12.13
Bwaise, x road	Commercial centre	Kampala	337.00	0.61	24.15	12.56
Kabowa - Gabunga Road	Residential unpaved (murrum) road	Kampala	338.07	0.59	23.00	11.96
Lungunja - Busega - Kibumbiro	Residential unpaved (murrum) road	Kampala	335.00	0.50	19.71	10.25
Rippon Garden - Nile Avenue	Residential/office paved (tarmac) road	Jinja	337.07	0.49	19.25	10.01
School Village - Tenywa Road Walukuba East	Residential unpaved (murrum) road	Jinja	336.83	0.27	10.48	5.45
Walukuba - Masese Road	Commercial centre	Jinja	336.42	0.29	11.14	5.79
Mulago Hill road 1	Commercial centre	Kampala	343.55	0.59	22.79	11.85
Mulago Hill road 2	Commercial centre	Kampala	311.63	0.78	31.78	16.53
Bugolobi	Residential/office paved (tarmac) road	Kampala	336.63	0.39	15.23	7.92
Banda Zone B8 - Banda Nalya Road	Commercial centre	Kampala	332.48	0.68	27.22	14.15
Namugongo Road, Kireka	Commercial centre	Kampala	332.45	1.31	52.90	27.51
Katanga, Wandegaya	Commercial centre	Kampala	331.50	0.81	32.72	17.02
Kawempe - Mbogo Road	Residential/office paved (tarmac) road	Kampala	333.50	0.61	24.14	12.55
Nansana - Nalvule	Residential unpaved (murrum) road	Kampala	332.42	0.53	21.26	22.70
Mbuya - Nadiopo	Residential/office paved (tarmac) road	Kampala	215.05	0.24	14.63	15.22
Lourdel road, Wandegaya	Commercial centre	Kampala	360.00	1.13	42.08	21.88
Kamwokya - Kyebando Rd	Commercial centre	Kampala	336.92	0.79	31.22	16.23
Kyanja - Nazereth Rd/Kyanja Road	Residential unpaved (murrum) road	Kampala	356.12	0.57	21.19	11.02
5th Street Industrial Area	Industrial area	Kampala	334.02	0.67	26.67	13.87
Nizam Road, Jinja centre	Commercial centre	Jinja	335.50	0.69	27.37	14.23
Industrial Area-Jinja	Industrial area	Jinja	338.15	0.47	18.53	9.64

Table S3. Concentration of Sulphur dioxide at sites with detectable Sulphur dioxide concentrations

Site	Land use	City	Exposure	Total (µg)	SO2	SO2 (µg/m³)	SO2 ppb
Kabowa - Gabunga Road	Residential unpaved (murrum) road	Kampala	338.07	0.05	2.34	0.88	
Mulago Hill road 1	Commercial centre	Kampala	311.63	0.04	1.73	0.65	
Bugolobi	Residential/office paved (tarmac) road	Kampala	336.63	0.04	1.81	0.68	
Banda Zone B8 - Banda Nalya Road	Commercial centre	Kampala	332.48	0.1	8.35	3.13	
Namugongo Road – Kireka road	Commercial centre	Kampala	332.45	0.03	0.77	0.29	
Kawempe - Mbogo Road	Residential/office paved (tarmac) road	Kampala	333.5	0.06	3.65	1.37	
Industrial Area-Jinja	Industrial area	Jinja	338.15	0.09	7.31	2.74	

CHAPTER 8: Lung Function of Children at Three Sites of Varying Ambient Air Pollution Levels in Uganda: A Cross Sectional Comparative Study

Authors

Bruce J. Kirenga^{1,2,3, *}, Rebecca Nantanda², Corina de Jong³, Levicatus Mugenyi², Qingyu Meng⁴, Gilbert Aniku⁵, Sian Williams⁶, Hellen Aanyu-Tukamuhebwa⁵, Moses Kamya¹, Stephan Schwander⁴, Thys van der Molen³ and Vahid Mohsenin⁷

1. Department of Medicine, Makerere University, Kampala, Uganda; brucekirenga@yahoo.co.uk mkamya@infocom.co.ug
2. Makerere University Lung Institute, Kampala, Uganda; brucekirenga@yahoo.co.uk, mantanda@gmail.com (R.N.); lmugenyi005@gmail.com (L.M.)
3. GRIAC-Primary Care, Department of General Practice and Elderly Care, University of Groningen, University Medical Center Groningen, Groningen EB79, The Netherlands; Groningen Research Institute for Asthma and COPD (GRIAC), University of Groningen, University Medical Center Groningen, Groningen EB79, The Netherlands; c.de.jong02@umcg.nl (C.d.J.); thys.v.molen@gsk.com (T.v.d.M.)
4. Departments of Urban-Global Public Health and Environmental and Occupational Health, School of Public Health, Rutgers University, The State University of New Jersey, Piscataway, NJ 08854, USA; Qingyu.Meng@dtsc.ca.gov (Q.M.); schwansk@sph.rutgers.edu (S.S.)
5. Department of Paediatrics and Child Health, Makerere University College of Health Sciences, Kampala, Uganda; gilbert.aniku@gmail.com (G.A.); hellen.aanyut@gmail.com (H.A.-T.)
6. International Primary Care Respiratory Group; Aberdeen, AB32 9AE, UK; sian.health@gmail.com
7. Department of Medicine, Yale University School of Medicine, New Haven, CT 06520, USA; vahid.mohsenin@yale.edu

* Correspondence: brucekirenga@yahoo.co.uk; Tel.: +256-782-404-431

Published in **Int. J. Environ. Res. Public Health** **2018**, **15**, 2653

ABSTRACT

Air pollution is a major cause of sub-optimal lung function and lung diseases in childhood and adulthood. In this study we compared the lung function (measured by spirometry) of 537 Ugandan children, mean age 11.1 years in sites with high (Kampala and Jinja) and low (Buwenge) ambient air pollution levels, based on the concentrations of particulate matter smaller than 2.5micrometres in diameter ($PM_{2.5}$). Factors associated with lung function were explored in a multiple linear regression model. $PM_{2.5}$ level in Kampala, Jinja and Buwenge were $177.5 \mu g/m^3$, $96.3 \mu g/m^3$ and $31.4 \mu g/m^3$ respectively ($p = 0.0000$). Respectively mean forced vital capacity as % of predicted (FVC%), forced expiratory volume in one second as % of predicted ($FEV_1\%$) and forced expiratory flow 25–75% as % of predicted ($FEF_{25-75}\%$) of children in high ambient air pollution sites (Kampala and Jinja) vs. those in the low ambient air pollution site (Buwenge subcounty) were: FVC% (101.4%, vs. 104.0%, $p = 0.043$), $FEV_1\%$ (93.9% vs. 98.0, $p = 0.001$) and $FEF_{25-75}\%$ (87.8 vs. 94.0, $p = 0.002$). The proportions of children whose % predicted parameters were less than 80% predicted (abnormal) were higher among children living in high ambient air pollution than those living in lower low ambient air pollutions areas with the exception of FVC%; high vs. low: $FEV_1 < 80\%$, %predicted (12.0% vs. 5.3%, $p = 0.021$) and $FEF_{25-75} < 80\%$, %predicted (37.7% vs. 29.3%, $p = 0.052$) Factors associated with lung function were (coefficient, p -value): FVC% urban residence (-3.87 , $p = 0.004$), current cough (-2.65 , $p = 0.048$), underweight (-6.62 , $p = 0.000$), and overweight (11.15, $p = 0.000$); $FEV_1\%$ underweight (-6.54 , $p = 0.000$) and $FEF_{25-75}\%$ urban residence (-8.67 , $p = 0.030$) and exposure to biomass smoke (-7.48 , $p = 0.027$). Children in study sites with high ambient air pollution had lower lung function than those in sites with low ambient air pollution. Urban residence, underweight, exposure to biomass smoke and cough were associated with lower lung function.

8.1 INTRODUCTION

Lung development commences in utero, continues through adolescence, and ceases in early adulthood (about 25 years).¹⁻³ During this stage of growth and development, several factors such as air pollution, may affect the lungs leading to sub-optimal lung function. Sub-optimal lung function predisposes to wheezing illness as children and Chronic Obstructive Pulmonary Disease (COPD) as adults.⁴⁻⁷ A study by Bui et al. that investigated the impact of childhood lung function deficits on adulthood COPD found that children in the lowest quartile of FEV₁/FVC ratio at 7 years had almost six times the risk of COPD in middle life.⁶ Prominent among the risk factors for early life lung damage is air pollution. Air pollution has the potential to impair lung growth from as early as prenatal life.⁸⁻¹⁰ Children are prone to greater lung damage from air pollution than adults because of their rapidly growing and still immature lungs, more time spent outdoors and increased physical activity requiring larger inhalation volumes.¹¹ Studies conducted in countries other than Uganda have reported deficits in lung function and increased frequency of respiratory symptoms in children of all age groups who are exposed to air pollution.^{14, 16-20} Urban-rural comparisons have reported a higher frequency of respiratory symptoms and poorer lung function among the urban children.¹²⁻¹⁴ One of the possible explanations is the higher degree of air pollution in the urban areas, arising from a combination of motor vehicle fumes, industries and biomass smoke arising from open rubbish burning and cooking and lighting in crowded slum areas in Low and Middle-income countries (LMICs). Like many other developing countries, Uganda is currently facing major challenges from increasing ambient and indoor air pollution levels.¹⁵⁻¹⁷ Recently, we reported mean ambient PM_{2.5} levels in two Ugandan cities which were 5.3 times than the World Health Organization (WHO) limits.¹⁵ Furthermore, we found that PM_{2.5} levels were higher in Kampala (the capital city) than in Jinja (the second largest city in Uganda) (138.6 µg/m³ vs. 99.3 µg/m³).¹⁵

We therefore hypothesized that children living in sites with high ambient air pollution (Kampala city and Jinja municipality, urban) would have lower lung function than those living the site with low ambient air pollution (Buwenge subcounty, rural). We also hypothesized that children in Jinja municipality which is a smaller city with lower ambient air pollution would have better lung function than those in Kampala city which has higher ambient air pollution. To test these hypotheses, we studied children at three sites of varying air pollution levels and urbanization in Uganda: Kampala (city), Jinja (municipality) and Buwenge subcounty (rural).

8.2 MATERIALS AND METHODS

This was a cross sectional survey of school children in two urban locations: (Kampala city, Jinja municipality) and one rural site (Buwenge subcounty in Jinja district).

Kampala city is the capital city of Uganda. It is characterized by a mixture of residences, industries and commercial areas. The residents are also a mixture of high, middle and low socioeconomic status. The middle and lower class commonly use biomass for cooking, particularly in form of charcoal and wood. Jinja municipality has demographic characteristics similar to those of Kampala city but on a lower scale; the population is smaller, less vehicular traffic and fewer slums. On the hand, Buwenge subcounty, which is found in the Jinja district, is a rural area, with little vehicular traffic and residents mainly use biomass for cooking using the typical three-stone open fire stoves.^{18,19} The main economic activity in Buwenge subcounty is subsistence agriculture and there are no industries.

The inhabitants of Kampala city and Jinja municipality are mainly Black Africans (99%), and the rest are either Asians or Caucasians. The people from Buwenge subcounty are all Black Africans.²⁰ The weather conditions in the three sites are almost the same with high temperatures and high humidity all year round. The average annual temperature is 21.9 °C and relative humidity ranges from 53–89%.²¹ Annual rainfall ranges from 1750–2000 mm. The survey in Jinja municipality and Buwenge subcounty was conducted during the March–April period which is the beginning of the first rainy season (relatively little rainfall). On the other hand, we tested Kampala children during the June–July period which is the end of the first rainy season (also relatively little rain).

The study was conducted in primary schools that were randomly selected from a list obtained from the district education departments. In Kampala, the schools selected were Buganda Road primary school and Uganda Railways primary school, both in the central division of Kampala. In Jinja municipality, Victoria Nile primary school and Walukuba East primary school were selected. In Buwenge subcounty, we randomly selected Buweera and Kagoma primary schools. All the schools that were selected are day public schools. The children in public schools in both urban and rural areas are usually from the lower socioeconomic class.

8.2.1 Sample Size

The sample size calculations were based on power ≥ 0.80 and two-sided $\alpha = 0.05$. The values used to calculate the sample size were based on estimates obtained from Asgari et al. study in Tehran.¹² We powered the study to detect a 6% difference in predicted percent FEV₁ between urban and rural areas. Two hundred participants were needed in each of the three sites (Kampala, Jinja urban and Jinja rural) to detect this difference.

8.2.2 Recruitment

Children in primary grades four to seven (commonly 9–12 years old) in the selected schools were all invited to participate in the study. Information about the study and consent forms were sent to the parents/guardians through the children, who provided written consent to their children's participation in the study. The children provided written assent. All participants were screened for any contraindication to spirometry (history of any mental illnesses, history of admission for cardiac illness within the last 6 months, recent thoracic, abdominal or eye surgery or retinal detachment and active tuberculosis or any other acute lung infection). Those who were found to have any contra-indications were excluded. Children with lung infections other than tuberculosis were later included upon recovery from the infection.

8.2.3. Data collection/Procedures

A questionnaire was used to collect data on the respiratory symptoms and air pollution exposures. Children completed the questionnaire with the help of their parents or a research assistant. Data on respiratory symptoms such as wheeze, cough and breathlessness at the time of data collection and/or in the 12 months prior to enrolment were also collected. Data on indoor and outdoor air pollution exposures such as exposure to biomass smoke while cooking, burning rubbish, and second-hand tobacco smoke was also collected.

Lung function assessment: Lung function was assessed by Spirometry according to American Thoracic

Society/European Respiratory Society (ATS/ERS) guidelines using a Pneumotrac[®] with Spirotrac[®] V software (Vitalograph Ltd., Buckingham, UK).²² Forced vital capacity (FVC), forced expiratory volume in the first second (FEV₁) and forced expiratory flow at 25–75% of FVC (FEF_{25–75}) and their corresponding percent predicted (%predicted) for age, weight, height, gender and ethnicity were recorded. Predicted parameters were based on NHANES III lung function prediction models.²³

Particulate pollutant measurement: PM_{2.5} concentrations were measured as an indicator of ambient air pollution. A real-time aerosol monitor, DUSTTRACK II-8530 (TSI Inc., Shoreview, MN, USA) was used to collect PM_{2.5} particle levels at each school (two schools per site). Sampling was done over 24 h for one day.

8.2.4. Data Analysis

Descriptive statistics were used to summarize the participants' socio-demographic characteristics and lung function parameters (forced vital capacity (FVC), forced expiratory volume in the first second (FEV₁), FEV₁/FVC (FEV₁ ratio) and forced expiratory flow 25–75% (FEF_{25–75}%) and their percentage predicted values (FVC%, FEV₁%, FEF_{25–75}%). These parameters were compared between sites using analysis of variance (ANOVA) and by urban status using the independent t-test. Urban residence was defined as residing in either Kampala city or Jinja municipality while rural residence was defined as residing in Buwenge subcounty.

We analyzed for factors associated with lung function, that is, factors associated with each of percentage predicted values (FVC%, FEV₁%, FEF_{25–75}%). First, we performed simple linear regression. Factors that showed an association with the parameters with a *p*-value of ≤ 0.20 were all included in a multiple linear regression model. The factors assessed for association were; (1) urban status (2) Air pollution:- ambient air pollution (PM_{2.5}, living within 500 m of a factory, living within 500 m of a road frequently used by cars) and exposure to biomass smoke (defined as using either charcoal, wood or kerosene in the homes for cooking or lighting), (3) tobacco smoke exposure defined as living with someone who smokes or children smoking themselves, (4) malnutrition (underweight and overweight) assessed by body mass index (BMI) for age. BMI for age was calculated using United States of America Centers for Disease Control and prevention software (children BMI tools for school),²¹ (5) socioeconomic status (SES) and (6) respiratory symptoms. The SES was assessed by SES index derivation from socioeconomic parameters collected in the survey using principal component analysis (PCA) as has been previously done in other studies.²⁴ The variables included in the PCA analysis were occupation of parents, education level of parents, type of housing, ownership of assets and number of persons sharing a room in the household. The SES was put in 3 quintiles with the lower quintile corresponding to lower values of the index and upper quintiles corresponding to the well-off households/individuals. Age, sex and height were not included in the model for factors associated with lung function because these are corrected for in the percentage predicted parameters. Correlation between factors (multicollinearity) was checked using variance inflation factor (VIF) and centering considering in case of a multicollinearity problem (VIF > 10). A *p*-value of less than 0.05 was considered to represent significant association. All analyses were performed using Stata version 14 (StataCorp. 2015. Stata Statistical Software: Release 14, StataCorp LP, College Station, TX, USA).

8.2.5. Ethical Considerations

The study protocol was approved by the Mulago Hospital Research and Ethics Committee and the Uganda National Council for Science and Technology. Administrative clearance was obtained from the departments of Education of Kampala city and Jinja district (ethical approval number: MREC:582). Parents/guardians provided informed written consent and children gave assent.

8.3 RESULTS

8.3.1. Study Participants Characteristics

Of the 537 participants, 185 were from Kampala, 151 from Jinja Municipality and 201 from Buwenge subcounty. The survey in Jinja and Buwenge was conducted in the months of March–April 2015 (beginning of rainy season) while that in Kampala was conducted in the months of June–July 2015 (end of rainy season). Children characteristics are presented in Table 1. The mean age (standard deviation) of the children was 11.1 ± 1.3 years. The proportion of boys was 44.3% in Kampala city, 33.1% in Jinja Municipality and 54.2% in Buwenge subcounty. The mean height of urban children was significantly higher than for rural children (145.5 cm for Kampala, 144.8 cm for Jinja municipality and 139.5 cm for Buwenge subcounty, $p = 0.0000$). Urban children weighed on average 36.2 kg (36.7 kg for Kampala and 35.7 kg for Jinja municipality) compared to rural children who weighed 32.1 kg, $p = 0.0000$. Underweight rates were 10.9% for Kampala, 17.3% for Jinja and 31.5% for Buwenge. Overweight rates were 8.2% for Kampala, 2.7% for Jinja and 5.6% for Buwenge. Obesity rates were low 0.5%, 3.3% and 0.5% for Kampala, Jinja and Buwenge respectively. Having one or more of the respiratory symptoms (cough, wheeze, shortness of breath) occurred in 54.1% of the children in Kampala, 62.9% of the children in Jinja municipality and 66.7% of the children in Buwenge subcounty ($p = 0.035$).

Table 1. Characteristics of study participants by site.

Characteristic	Kampala City (<i>n</i> = 185)	Jinja Municipality (<i>n</i> = 151)	Buwenge Sub- county (<i>n</i> = 201)	<i>p</i> -Value
<i>Socio-demographics</i>				
Age, Mean (SD)	11.3 (1.3)	11.0 (1.3)	11.0 (1.3)	0.2375
Gender				
Boys, (%)	44.3	33.1	54.2	0.001
Occupation of father				0.000
Professional	36.8	32.9	11.4	
Unemployed	2.7	4.1	8.3	
Peasant farmer	7.0	9.6	47.7	
Market vendor	4.9	8.2	7.3	
Builder	4.9	6.8	7.8	
Clerical worker (sales clerk, secretaries, driver etc.)	4.9	15.7	5.7	
Other	38.9	22.6	11.9	
<i>Anthropometry</i>				
Height (cm), mean (SD)	145.5 (10.0)	144.8 (8.6)	139.5 (11.6)	0.0000
Weight (kg), mean (SD)	36.7 (8.7)	35.7 (8.4)	32.1 (9.8)	0.0000
BMI categories				0.000
Underweight (BMI < 5%), %	10.9	17.3	31.5	
Normal (BMI: 5–85%), %	80.4	76.7	62.4	
Overweight (BMI: 85–95%), %	8.2	2.7	5.6	
Obese (BMI > 95%), %	0.5	3.3	0.5	
<i>Respiratory symptoms</i>				
Currently coughs several times a day, % (95% CI)	46.0 (38.7–53.2)	51.7 (43.5–59.9)	61.0 (54.2–67.9)	0.012
Wheeze% (95% CI)	23.2 (17.1–29.4)	30.7 (23.3–38.1)	21.6 (15.7–27.5)	0.131
Shortness of breath (get out of breath more easily than others), % (95% CI)	26.1 (19.7–32.5)	24.4 (17.0–31.8)	28.6 (22.0–35.2)	0.703
Has at least one respiratory symptom	54.1 (46.8–61.3)	62.9 (55.2–70.7)	66.7 (60.1–73.2)	0.035

8. 3.2. Air Pollution

Air pollution exposures (indoor and outdoor) are shown in Table 2. Children had high exposures to biomass smoke in both urban and rural sites, but higher among rural children (94.6% vs. 87.1%, $p = 0.011$). Exposure to second hand tobacco smoke was higher among rural than urban children (6.2% vs. 3.0%, $p = 0.11$). The mean particulate matter pollution ($PM_{2.5}$) levels by site are shown in Table 2. The 24-h pollution levels for Kampala city, Jinja municipality and Buwenge subcounty were 177.5 $\mu\text{g}/\text{m}^3$, 96.3 $\mu\text{g}/\text{m}^3$ and 31.4 $\mu\text{g}/\text{m}^3$ respectively ($p = 0.0000$).

Table 2. Air pollution exposures by site.

Characteristic	Kampala City (n = 185)	Jinja Municipality (n = 151)	Buwenge Sub- county (n = 201)	p-Value
<i>Particulate air pollutant levels in surveyed schools</i>				
PM_{2.5} particle levels (Minimum/Maximum)	62.5/424	30.0/236.5	16/101.5	0.0000
PM _{2.5} particle levels 24 h average, mean (SD), µg/m ³	177.5 (43.9)	96.3(9.5)	31.4 (12.2)	0.0000
<i>Exposure to tobacco smoke</i>				
Parental current smoker (%)	4.9	0.0	4.0	0.031
Stay/live with smoker (%)	30.9	14.6	30.9	0.001
<i>Exposure to biomass smoke</i>				
Exposed to biomass used indoors (%)	83.6	92.7	94.6	0.002
Use wood for cooking/lighting (%)	16.7	51.9	97.8	0.000
Use charcoal for cooking/lighting (%)	96.1	97.9	67.9	0.000
Use kerosene for cooking/lighting (%)	23.6	30.4	36.2	0.221
Outdoor rubbish burning near home (%)	48.6	90.8	77.7	0.000
Exposed to bush burning (self/others) (%)	13.8	48.9	55.6	0.000
Lives within 500 m of industry (%)	16.1	48.9	40.7	0.000
Lives within 500 m of road used by cars(%)	89.7	79.5	73.1	0.000

8.3.3. Lung Function

Lung function data are presented in Tables 3–5 and Figure 1. The mean FVC, FEV₁, FEF_{25–75} % in liters for children in Kampala, Jinja and Buwenge were as follows: FVC 2.2, 2.1, 2.0, ($p = 0.0001$), FEV₁ 2.0, 1.9, 1.8, ($p = 0.0002$) and FEF_{25–75} % 2.6, 2.5, 2.5, ($p = 0.3704$) respectively. In addition, FEV₁ ratios for Kampala, Jinja and Buwenge were 0.90, 0.91 and 0.91 respectively. The percentage predicted parameters, for Kampala, Jinja and Buwenge were: FVC% 103.7%, 98.6%, 104.0%; ($p = 0.034$), FEV₁ % 95.6%, 91.8%, 99.2% ($p = 0.000$), FEF_{25–75} % 88.1%, 87.4%, 94.6% ($p = 0.032$) as highlighted in Table 3. When grouped by urban status (high vs. low air pollution levels), the actual lung function values for urban children appeared higher than for rural children but after correcting for age, height, sex (the percentage predicted parameters) rural children were found to have significantly better lung function than urban children (Table 4 and Figure 1b). A comparison the same parameters between Kampala and Jinja municipality (the two urban sites) revealed that Kampala children had higher parameters than Jinja municipality children with the exception of FEF_{25–75} % where the differences where not statistically different (Table 5). The proportions of children whose % predicted parameters were less than 80% predicted by urban status urban vs. rural were: FVC < 80%, %predicted (3.3% vs. 3.0%, $p = 0.85$), FEV₁ < 80%, %predicted (12.0% vs. 5.8%, $p = 0.021$) and FEF_{25–75} < 80%, %predicted (37.7% vs. 29.3%, $p = 0.052$) (Table 5).

Table 3. Lung function of study participants by site.

Characteristic	By Site			
	Kampala City (<i>n</i> = 185)	Jinja Municipality (<i>n</i> = 151)	Buwenge Sub- county (<i>n</i> = 201)	<i>p</i> -Value
Actual lung function parameters of children unadjusted for their age, sex, and height				
FVC (L), mean (SD)	2.2 (0.5)	2.1 (0.4)	2.0 (0.5)	0.0001
FEV ₁ (L), mean (SD)	2.0 (0.5)	1.9 (0.5)	1.8 (0.4)	0.0002
FEV1/FVC ratio, mean (SD)	0.90 (0.09)	0.91 (0.06)	0.91 (0.05)	0.000
FEF ₂₅₋₇₅ (mL), mean (SD)	2.6 (0.7)	2.5 (0.7)	2.5 (0.7)	0.3704
Percentage of predicted lung function				
FVC% predicted, mean (SD)	103.7 (15.1)	98.6 (12.4)	104.0 (13.3)	0.034
FEV1 % predicted, mean (SD)	95.6 (13.5)	91.8 (11.9)	98.0 (13.0)	0.000
FEF ₂₅₋₇₅ predicted, mean (SD)	88.1 (19.9)	87.4 (21.5)	94.0 (22.8)	0.006
FVC < 80%, <i>n</i> (%)	5 (2.8)	6 (4.1)	6 (3.1)	0.777
FEV1 < 80%, <i>n</i> (%)	21 (11.6)	18 (12.4)	11 (5.8)	0.068
FEF ₂₅₋₇₅ < 80%, <i>n</i> (%)	65 (35.9)	58 (40.0)	56 (29.3)	0.113
FEV1/FVC ratio < 0.7, <i>n</i> (%)	1 (0.6)	0 (0.0)	0 (0.0)	0.629

Table 4. Lung function and lung function abnormalities of study participants by urban status.

Characteristic	Urban (n = 336)	Rural (n = 201)	p-Value
Actual lung of children unadjusted for their age, sex, and height			
FVC (L), mean (SD)	2.2 (0.5)	2.0 (0.5)	0.0006
FEV ₁ (L), mean (SD)	2.0 (0.4)	1.8 (0.4)	0.001
FEV1/FVC ratio, mean (SD)	0.90 (0.05)	0.91 (0.05)	0.039
FEF ₂₅₋₇₅ (mL), mean (SD)	2.6 (0.7)	2.5 (0.7)	0.269
FVC% predicted, mean (SD)	101.4 (14.2)	104.0 (13.3)	0.043
FEV1 % predicted, mean (SD)	93.9 (12.9)	98.0 (13.0)	0.001
FEF ₂₅₋₇₅ predicted, mean (SD)	87.8 (20.6)	94.0 (22.8)	0.002
FVC < 80%, n (%)	11 (3.4)	6 (3.1)	0.878
FEV1 < 80%, n (%)	39 (12.0)	11 (5.8)	0.021
FEF ₂₅₋₇₅ < 80%, n (%)	123 (37.7)	56 (29.3)	0.052
FEV1/FVC ratio < 0.7, n (%)	1 (0.3)	0 (0.0)	0.629

Table 5. Lung function of study participants comparing Kampala city and Jinja municipality.

Characteristic	Kampala City (n = 185)	Jinja Municipality (n = 151)	p-Value
Actual lung of children unadjusted for their age, sex, and height			
FVC (L), mean (SD)	2.2 (0.5)	2.1 (0.4)	0.004
FEV ₁ (L), mean (SD)	2.0 (0.5)	1.9 (0.5)	0.011
FEV1/FVC ratio, mean (SD)	0.90 (0.09)	0.91 (0.06)	0.059
FEF ₂₅₋₇₅ (mL), mean (SD)	2.6 (0.7)	2.5 (0.7)	0.389
FVC% predicted, mean (SD)	103.7 (15.1)	98.6 (12.4)	0.002
FEV1 % predicted, mean (SD)	95.6 (13.5)	91.8 (11.9)	0.008
FEF ₂₅₋₇₅ predicted, mean (SD)	88.1 (19.9)	87.4 (21.5)	0.779
FVC < 80%, n (%)	5 (2.8)	6 (4.1)	0.494
FEV1 < 80%, n (%)	21 (11.6)	18 (12.4)	0.822
FEF ₂₅₋₇₅ < 80%, n (%)	65 (35.9)	58 (40.0)	0.449
FEV1/FVC ratio < 0.7, n (%)	1 (0.6)	0.0	0.555

Figure 1. Mean distribution of spirometry parameters (percentage of predicted lung function) by site (1a) and (1b). By urban status (1b). Circles show mean levels and bars show standard deviation. FVC = forced vital capacity, FEV₁ = forced expiratory volume in one second and FEF = forced expiratory flow 25–75%.

8.3.4. Factors Associated with Lung Function

Factors associated with each of the lung function parameter (FVC%, FEV₁% and FEF_{25–75}%) in a multivariate linear model are presented in Table 6. Significant associations were observed with the following factors: FVC% rural residence (3.87, $p = 0.004$), underweight (−6.62, $p = 0.000$), overweight (11.15, $p = 0.000$) and cough (−2.65, $p = 0.048$); FEV₁% underweight (−6.54, $p = 0.001$) and FEF_{25–75}% rural residence (8.67, $p = 0.030$) and exposure to biomass smoke (−7.48, $p = 0.027$).

Table 6. Factors associated with FVC%, FEV₁% and FEF₂₅₋₇₅% at multivariate stage.

Factor	Coefficient	95% CI	p-Value
FVC%			
Residence (ref. Urban)			
Rural	3.87	1.25–6.50	0.004
Lives within 500 m of industry	–1.28	–3.90–1.35	0.340
BMI (ref. normal):			
Under-weight	–6.62	–9.74––3.50	0.000
Over-weight	11.15	5.55–16.75	0.000
Obese	10.44	–1.46–22.35	0.085
Current coughs several times a day	–2.65	–5.28––0.02	0.048
Wheeze	0.09	–2.98–3.16	0.953
FEV ₁ %			
Residence (ref. Urban)			
Rural	5.46	–0.10–11.02	0.054
PM _{2.5} particle levels 24 h average, µg/m ³	–0.01	–0.05–0.02	0.491
Lives within 500 m of industry	–2.49	–5.73–0.75	0.132
BMI (ref. normal):			
Under-weight	–6.54	–10.26––2.82	0.001
Over-weight	4.84	–1.91–11.56	0.160
Obese	9.53	–5.05–24.11	0.200
SES (ref. high):			
Low	–0.96	–6.46–4.54	0.732
Middle	–3.28	–7.19–0.63	0.100
FEF ₂₅₋₇₅ %			
Residence (ref. Urban)			
Rural	8.67	0.8–16.49	0.030
PM _{2.5} particle levels 24 h average †, µg/m ³	0.01	–0.04–0.06	0.709
Rubbish/bush burning	4.21	–0.42–8.85	0.075
Exposure to biomass smoke	–7.48	–14.09––0.86	0.027
Wheeze	4.52	–0.08–9.12	0.054
BMI (ref. normal):			
Under-weight	–3.71	–8.76–1.34	0.149
Over-weight	0.28	–8.71–9.28	0.951
Obese	6.55	–12.96–26.07	0.510
SES (ref. high):			
Low	1.03	–6.47–8.54	0.787
Middle	–3.33	–8.47–1.81	0.204

† Centered around the mean (mean for PM_{2.5} = 100).

4. DISCUSSION

Results from this study show that children living in urban areas with high air pollution have significantly lower lung function and higher rates of failure to reach at least 80% of their predicted lung function than those living in less polluted rural areas. Lower lung function is associated with urban residence, underweight, cough and exposure to biomass smoke.

The finding of lower lung function in children exposed to high levels of air pollution is similar to findings from previous studies in other settings such as Greece, India and Iran.¹²⁻¹⁴ A study by Asgari et al. found mean FEV₁% of 89.0% in high ambient air pollution location and 99.0% in a low ambient air pollution areas.¹² In California a 10-year prospective study found deficits in FEV₁ growth to be associated with pollution.²⁵ A follow up study in this cohort has confirmed significant improvements in lung function with decreasing air pollution (mean 4-year growth in FEV₁ increased by 91.4 ml per decrease of 14.1 ppb in nitrogen dioxide level ($p < 0.001$), by 65.5 mL per decrease of 8.7 µg per cubic meter in PM₁₀ level ($p < 0.001$), and by 65.5 mL per decrease of 12.6 µg per cubic meter in PM_{2.5} level ($p = 0.008$)).²⁶ These findings suggest a deleterious effect of air pollution on children lung function.^{9, 27-29} Air pollution exposure is believed to result in a reduced formation of alveoli and causes inflammation that leads to airway remodeling eventually resulting in reduced lung function.³⁰

It must be noted that the differences in the percentage predicted parameters in our study between urban and rural children though statistically significant are much lower than observed in other studies. We found that FVC% was only 2.6% lower, FEV₁% was 5.3% lower and FEF₂₅₋₇₅% was 6.8% lower compared to the ones reported by Asgari et al. and other studies. We postulate that these smaller differences could be due to higher exposure of rural children to indoor air pollution due to more frequent use of wood for indoor cooking. Indoor air pollution exposure has also been linked to decrement in lung function. In China Roy et al. found a mean FEV₁ of 1427 mL SD 303 mL among children exposed to biomass smoke and 1598 mL SD 325 mL among those not exposed to biomass smoke, a difference of 171 mL (10.7%).³¹

Although the association between lung function and air pollution (PM_{2.5}) in this study did not reach statistical significance, the lower lung function in urban children in study is probably due to exposure to ambient air pollution. The average PM_{2.5} levels measured at the urban site of 141.0 µg/m³ far exceeds World Health Organization (WHO) defined allowable limits of 25 µg/m³. This is not the first study demonstrating high pollution levels in the study urban sites. In our study conducted in 2014 we demonstrated average levels of PM_{2.5} particles of 132.1 µg/m³ in Kampala and Jinja.¹⁵

The study found that children in Jinja municipality had lower lung function than those in Kampala city which has higher ambient air pollution. We expected that lung function would be lowest in Kampala children followed by Jinja municipality and Buwenge. The reasons for this observation are not clear from the data that we have from the survey. However, we think that it probably due to the fact that Jinja municipality's air pollution was much higher than recommended (96.3 µg/m³) and also had higher rates of biomass smoke exposure than Kampala city (92.7% vs. 83.6%) as well as higher rates of underweight (17.3% vs. 10.9%) and cough (51.7% vs. 46.0%).

In addition to lower attainment of expected lung function, this study found that the rates of abnormal lung function as assessed by having an FEV₁% and FEF₂₅₋₇₅% less than 80% predicted was higher among children in high pollution urban sites. These two lung function parameters assess air narrowing or obstruction. Indeed, in children FEF₂₅₋₇₅ is believed to be a better measure of airway obstruction than the FVC/FEV₁.³² The abnormalities could also be reflection higher asthma which is known to be more prevalent in urban areas.^{33, 34} A study by Churg et al. of 20 children exposed to high air pollution in Mexico City and 20 Canadian children with low exposure to particle pollution found that Mexican children had more small airway fibrous tissue and electron microscope found high burden of particles in

Mexican children with some having visible particles in the mucosa.^{30, 35, 36}

Children in urban sites, those with cough, exposure to biomass smoke and underweight had lower lung function. The association between lung function and, cough, urbanization, underweight and biomass smoke exposure has been previously reported.^{15, 37-39} In the current study, the association between biomass smoke exposure and lung function was found only for FEF₂₅₋₇₅%, a key marker of small airway dysfunction. The pathophysiology of biomass smoke airway damage is not yet fully understood but a recent study in China suggests that biomass smoke probably causes disease through damage to the small airways which is consistent with the association with FEF₂₅₋₇₅% observed in this study [40]. Nutritional status has been previously found to affect lung function.^{39, 41-43} In Nigeria, Kuti et al. assessed the effect of nutritional status in 250 children and found that underweight children had significantly lower lung function than normal weight children.³⁹ Overweight is usually associated with lower lung function. The association with overweight is probably a reflection of better wellbeing in this cohort rather than a true association because we observed high rates of underweight in this study. The association between respiratory symptoms and lower function has been previously observed and may be a reflection obstructive disease such as asthma.^{44, 45} Bremner et al. in a study in Australia showed that persons with current cough has FEV₁ 65mls lower than those without cough.⁴⁵

This study did not assess physical activity which is known to affect lung function.^{46, 47} Jie Ji et al. in a study of 1713 Chinese girls (average age 9.9 years) found that physical activity as reported on a questionnaire was associated with better growth in mid expiratory flows per year (FEF₂₅₋₇₅, 0.36 L/s vs. 0.28 L/s) (all $p < 0.05$).⁴⁶ In another study Wang DY et al. found that lung function was positively correlated with fat free mass a surrogate of better physical activity.⁴⁷ In this study, we did not investigate physical activity and therefore cannot assess its effect on lung function. However, literature shows that rural children are usually more physically active than urban children.⁴⁸⁻⁵⁰

We found that respiratory symptoms were very common among children irrespective of whether they were from high pollution (urban) or low pollution (rural). Rural children had more cough while urban children had more wheeze. The observation is consistent with that observed in other studies.^{12, 51} Asgari et al. found a similar pattern in Tehran: lower function among urban children and more respiratory symptoms in rural children.¹² In Bangladesh a study reports that the children in the rural area suffered significantly more from respiratory symptoms (incidence rate ratio 1.63, 95% confidence interval (CI) 1.62–1.64).⁵¹ The higher symptom rate among rural children could probably be due to high indoor pollution exposure. Although overall exposure to biomass used for cooking, heating and lighting in homes was high among urban and rural children, use of biomass fuels such as wood which are known to be more polluting was higher among rural children. Exposure to biomass pollution for children occurs in very high levels during cooking and probably more associated with acute respiratory effects rather than the chronic lung function deficits. Previous studies have found associations between respiratory infections and exposure to indoor air pollution. These infections could cause more symptoms especially cough and phlegm which are indicative respiratory infection rather than permanent lung function deficit.⁵² Ambrose and Onyekachi analyzed Uganda demographic and health surveys of 2001 and 2011 respectively and found that acute respiratory infections were strongly associated with the use of biomass fuels in household settings.^{52, 53} Sanbata et al. also found that acute respiratory illness in children was correlated with living in poor housing circumstances characterized by greater biomass fuel use.⁵³ We

further postulate that the higher reports of respiratory symptoms among the rural children in the current study could be related to poor access to health care facilities in the rural settings. Symptomatic children in urban environments may be treated earlier due to better access to healthcare hence presenting fewer concurrent symptoms. It is well described that access to healthcare is usually poor in rural areas.^{54, 55}

Rural children were significantly shorter than urban children (145.2 cm vs. 139.5 cm). The finding that rural children are shorter has been reported in Uganda National demographic and health survey (UDHS) and the Uganda National panel surveys (UNPS).^{56, 57} In the UDHS stunting rate among under five children was 35.6% among rural children and 18.6% among urban children.⁵⁶ while in UNPS it was 35% vs. 15%.⁵⁷ This study did not involve a detailed assessment of factors associated with growth and nutrition. However other studies in Uganda investigating factors associated with stunting found that stunting was associated with poor health, low socioeconomic status of the family, poor education of the mother of infants < 12 months, consumption of food of low energy density (<350 kcal/100 g dry matter) and consumption of small meals.^{58, 59}

This survey had limitations. Firstly, the survey was not conducted simultaneously at the different sites and only one day PM_{2.5} measurements were conducted. There could have been temporal changes in air pollution levels that could affect the outcomes. Children in schools were included. Children in schools may be different from their counterparts out of school in terms of socio-economic status. School going may also increase person to person transmission of respiratory infections hence the high symptom rates. Objective assessment of indoor air pollution was not done. Therefore, the true exposure status of the children to indoor pollutants cannot be ascertained. We also did not perform a detailed nutritional assessment. Nutritional is known to affect lung function and health. The study is a cross sectional survey which limits ability to study factors that could be responsible for the lower lung function.

5. CONCLUSIONS

Children in study sites with high ambient air pollution had lower lung function than those in sites with low ambient air pollution. Urban residence, underweight, exposure to biomass smoke and cough were associated with lower lung function.

Author Contributions: The following are the author contributions; conceptualization and methodology, B.J.K., T.v.d.M., S.W., M.K. and V.M.; Data acquisition B.J.K., Q.M., S.S., G.A. & H.A.-T., Data analysis L.M., B.J.K., C.d.J. and R.N. B.J.K. drafted the original manuscript. All authors reviewed and edited the manuscript.

Funding: This research was funded by the International Primary Care Respiratory Group (IPCRG).

Acknowledgments: The authors wish to thank the International Primary Care Respiratory Group for funding the study. We thank Rogers Sekibira, Denis Senfuka, Shamim Buteme and Zephania Mangusho for managing the data. We thank the research assistants especially Stephen Wanyange who performed the spirometry, the children, teachers and their parents for participating in the study. Special thanks go to the school administration and district education administrators for providing clearance to undertake this study.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Thurlbeck, W. M., Postnatal human lung growth. *Thorax* **1982**, 37, (8), 564-571.
2. Thurlbeck, W. M., Postnatal Growth and Development of the Lung 1. *American Review of Respiratory Disease* **1975**, 111, (6), 803-844.
3. Kotecha, S., Lung growth for beginners. *Paediatric respiratory reviews* **2000**, 1, (4), 308-313.
4. Gray, D.; Willemse, L.; Visagie, A.; Czövek, D.; Nduru, P.; Vanker, A.; Stein, D. J.; Koen, N.; Sly, P. D.; Hantos, Z., Determinants of early-life lung function in African infants. *Thorax* **2016**, thoraxjnl-2015-207401.
5. Martinez, F. D., The origins of asthma and chronic obstructive pulmonary disease in early life. *Proceedings of the American Thoracic Society* **2009**, 6, (3), 272-277.
6. Bui, D. S.; Burgess, J. A.; Lowe, A. J.; Perret, J. L.; Lodge, C. J.; Bui, M.; Morrison, S.; Thompson, B. R.; Thomas, P. S.; Giles, G. G.; Garcia-Aymerich, J.; Jarvis, D.; Abramson, M. J.; Walters, E. H.; Matheson, M. C.; Dharmage, S. C., Childhood Lung Function Predicts Adult Chronic Obstructive Pulmonary Disease and Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome. *Am J Respir Crit Care Med* **2017**, 196, (1), 39-46.
7. Stern, D. A.; Morgan, W. J.; Wright, A. L.; Guerra, S.; Martinez, F. D., Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet* **2007**, 370, (9589), 758-64.
8. Wong, K.; Rowe, B.; Douwes, J.; Senthilselvan, A., International prevalence of asthma and wheeze in adults: Results from the world health survey. In *B47. ASTHMA EPIDEMIOLOGY: CLINICAL AND PHARMACOLOGICAL DETERMINANTS OF ASTHMA OUTCOMES*, Am Thoracic Soc: 2010; pp A3117-A3117.
9. Salvi, S., Health effects of ambient air pollution in children. *Paediatr Respir Rev* **2007**, 8, (4), 275-80.
10. Kajekar, R., Environmental factors and developmental outcomes in the lung. *Pharmacol Ther* **2007**, 114, (2), 129-45.
11. Bateson, T. F.; Schwartz, J., Children's response to air pollutants. *J Toxicol Environ Health A* **2008**, 71, (3), 238-43.
12. Asgari, M. M.; DuBois, A.; Asgari, M.; Gent, J.; Beckett, W. S., Association of ambient air quality with children's lung function in urban and rural Iran. *Archives of environmental health* **1998**, 53, (3), 222-30.
13. Priftis, K. N.; Anthracopoulos, M. B.; Paliatsos, A. G.; Tzavelas, G.; Nikolaou-Papanagiotou, A.; Douridas, P.; Nicolaidou, P.; Mantzouranis, E., Different effects of urban and rural environments in the respiratory status of Greek schoolchildren. *Respiratory medicine* **2007**, 101, (1), 98-106.
14. Sonnappa, S.; Lum, S.; Kirkby, J.; Bonner, R.; Wade, A.; Subramanya, V.; Lakshman, P. T.; Rajan, B.; Nooyi, S. C.; Stocks, J., Disparities in pulmonary function in healthy children across the Indian urban-rural continuum. *Am J Respir Crit Care Med* **2015**, 191, (1), 79-86.
15. Umoh, V. A.; Peters, E., The relationship between lung function and indoor air pollution among rural women in the Niger Delta region of Nigeria. *Lung India: Official Organ of Indian Chest Society* **2014**, 31, (2), 110.
16. Schwander, S.; Okello, C. D.; Freers, J.; Chow, J. C.; Watson, J. G.; Corry, M.; Meng, Q., Ambient particulate matter air pollution in Mpererwe District, Kampala, Uganda: a pilot study. *J Environ Public*

17. Wallner, P.; Kundi, M.; Moshhammer, H.; Piegler, K.; Hohenblum, P.; Scharf, S.; Fröhlich, M.; Damberger, B.; Tappler, P.; Hutter, H.-P., Indoor air in schools and lung function of Austrian school children. *Journal of environmental monitoring* **2012**, 14, (7), 1976-1982.
18. Jagger, P.; Shively, G., Land Use Change, Fuel Use and Respiratory Health in Uganda. *Energy policy* **2014**, 67, 713-726.
19. Van Gemert, F.; Kirenga, B.; Chavannes, N.; Kamya, M.; Luzige, S.; Musinguzi, P.; Turyagaruka, J.; Jones, R.; Tsiligianni, I.; Williams, S.; de Jong, C.; van der Molen, T., Prevalence of chronic obstructive pulmonary disease and associated risk factors in Uganda (FRESH AIR Uganda): a prospective cross-sectional observational study. *The Lancet. Global health* **2015**, 3, (1), e44-51.
20. Uganda Bureau of Statistics (UBOS) and ICF. *Uganda Demographic and Health Survey 2016: Key Indicators Report*; UBOS: Rockville, MD, USA; Kampala, Uganda, 2017.
21. Banda, H. T.; Mortimer, K.; Bello, G. A.; Mbera, G. B.; Namakhoma, I.; Thomson, R.; Nyirenda, M. J.; Faragher, B.; Madan, J.; Malmborg, R.; Stenberg, B.; Mpunga, J.; Mwangomba, B.; Gama, E.; Piddock, K.; Squire, S. B., Informal Health Provider and Practical Approach to Lung Health interventions to improve the detection of chronic airways disease and tuberculosis at primary care level in Malawi: study protocol for a randomised controlled trial. *Trials* **2015**, 16, 576.
22. Heinzerling, A. P.; Guarnieri, M. J.; Mann, J. K.; Diaz, J. V.; Thompson, L. M.; Diaz, A.; Bruce, N. G.; Smith, K. R.; Balmes, J. R., Lung function in woodsmoke-exposed Guatemalan children following a chimney stove intervention. *Thorax* **2016**, thoraxjnl-2015-207783.
23. 23. Hankinson, J. L.; Odencrantz, J. R.; Fedan, K. B., Spirometric reference values from a sample of the general US population. *American journal of respiratory and critical care medicine* **1999**, 159, (1), 179-187.
24. Vyas, S.; Kumaranayake, L., Constructing socio-economic status indices: how to use principal components analysis. *Health policy and planning* **2006**, 21, (6), 459-468.
25. Gauderman, W. J.; Gilliland, G. F.; Vora, H.; Avol, E.; Stram, D.; McConnell, R.; Thomas, D.; Lurmann, F.; Margolis, H. G.; Rappaport, E. B.; Berhane, K.; Peters, J. M., Association between air pollution and lung function growth in southern California children: results from a second cohort. *Am J Respir Crit Care Med* **2002**, 166, (1), 76-84.
26. Gauderman, W. J.; Urman, R.; Avol, E.; Berhane, K.; McConnell, R.; Rappaport, E.; Chang, R.; Lurmann, F.; Gilliland, F., Association of improved air quality with lung development in children. *New England Journal of Medicine* **2015**, 372, (10), 905-913.
27. Jedrychowski, W.; Flak, E.; Mroz, E., The adverse effect of low levels of ambient air pollutants on lung function growth in preadolescent children. *Environ Health Perspect* **1999**, 107, (8), 669-74.
28. Von Mutius, E.; Martinez, F. D.; Fritzsch, C.; Nicolai, T.; Roell, G.; Thiemann, H.-H., Prevalence of asthma and atopy in two areas of West and East Germany. *American journal of respiratory and critical care medicine* **1994**, 149, (2), 358-364.
29. Jedrychowski, W.; Flak, E.; Mróz, E., The adverse effect of low levels of ambient air pollutants on lung function growth in preadolescent children. *Environmental health perspectives* **1999**, 107, (8), 669.
30. Churg, A.; Brauer, M.; del Carmen Avila-Casado, M.; Fortoul, T. I.; Wright, J. L., Chronic exposure to high

- levels of particulate air pollution and small airway remodeling. *Environmental Health Perspectives* **2003**, 111, (5), 714.
31. Qian, Z.; He, Q.; Kong, L.; Xu, F.; Wei, F.; Chapman, R.; Chen, W.; Edwards, R.; Bascom, R., Respiratory responses to diverse indoor combustion air pollution sources. *Indoor Air* **2007**, 17, (2), 135-142.
 32. Rao, D. R.; Gaffin, J. M.; Baxi, S. N.; Sheehan, W. J.; Hoffman, E. B.; Phipatanakul, W., The utility of forced expiratory flow between 25% and 75% of vital capacity in predicting childhood asthma morbidity and severity. *Journal of Asthma* **2012**, 49, (6), 586-592.
 33. Nicolaou, N.; Siddique, N.; Custovic, A., Allergic disease in urban and rural populations: increasing prevalence with increasing urbanization. *Allergy* **2005**, 60, (11), 1357-1360.
 34. Yemaneberhan, H.; Bekele, Z.; Venn, A.; Lewis, S.; Parry, E.; Britton, J., Prevalence of wheeze and asthma and relation to atopy in urban and rural Ethiopia. *The lancet* **1997**, 350, (9071), 85-90.
 35. Souza, M. B.; Saldiva, P. H.; Pope, C. A.; Capelozzi, V. L., Respiratory changes due to long-term exposure to urban levels of air pollution: a histopathologic study in humans. *CHEST Journal* **1998**, 113, (5), 1312-1318.
 36. Abbey, D. E.; Burchette, R. J.; Knutsen, S. F.; McDonnell, W. F.; Lebowitz, M. D.; Enright, P. L., Long-term particulate and other air pollutants and lung function in nonsmokers. *American journal of respiratory and critical care medicine* **1998**, 158, (1), 289-298.
 37. Balcan, B.; Akan, S.; Ugurlu, A. O.; Handemir, B. O.; Ceyhan, B. B.; Ozkaya, S., Effects of biomass smoke on pulmonary functions: a case control study. *International journal of chronic obstructive pulmonary disease* **2016**, 11, 1615.
 38. Jiwtoode, M. T.; Raikar, P. R., Comparison of pulmonary function tests in urban and rural children of Nagpur, Maharashtra, India. *International Journal of Research in Medical Sciences* **2017**, 5, (3), 908-911.
 39. Kutu, B. P.; Oladimeji, O. I.; Kutu, D. K.; Adeniyi, A. T.; Adeniji, E. O.; Osundare, Y. J., Rural-urban disparity in lung function parameters of Nigerian children: effects of socio-economic, nutritional and housing factors. *Pan African Medical Journal* **2017**, 28, (230).
 40. Zhao, D.; Zhou, Y.; Jiang, C.; Zhao, Z.; He, F.; Ran, P., Small airway disease: A different phenotype of early stage COPD associated with biomass smoke exposure. *Respirology* **2017**.
 41. Glew, R.; Brock, H.; VanderVoort, J.; Agaba, P.; Harkins, M.; VanderJagta, D., Lung function and nutritional status of semi-nomadic Fulani children and adolescents in northern Nigeria. *Journal of tropical pediatrics* **2004**, 50, (1), 20-25.
 42. Harikumar, R.; Nair, C. K.; Shashidhar, S., Spirometric impairments in undernourished children. *Indian J Physiol Pharmacol* **1999**, 43, (4), 467-473.
 43. Obaseki, D. O.; Erhabor, G. E.; Awopeju, O. F.; Adewole, O. O.; Adeniyi, B. O.; Buist, E. A. S.; Burney, P. G., Reduced Forced Vital Capacity in an African Population. Prevalence and Risk Factors. *Annals of the American Thoracic Society* **2017**, 14, (5), 714-721.
 44. Langkulsen, U.; Jinsart, W.; Karita, K.; Yano, E., Respiratory symptoms and lung function in Bangkok school children. *The European Journal of Public Health* **2006**, 16, (6), 676-681.
 45. Bremner, P. R.; de KLERK, N. H.; Ryan, G. F.; James, A. L.; Musk, M.; Murray, C.; LE SŌUEF, P. N.; Young, S.; Spargo, R.; WILLIAM MUSK, A., Respiratory symptoms and lung function in aborigines from

- tropical Western Australia. *American journal of respiratory and critical care medicine* **1998**, 158, (6), 1724-1729.
46. Ji, J.; Wang, S.-q.; Liu, Y.-j.; He, Q.-q., Physical activity and lung function growth in a cohort of Chinese school children: a prospective study. *PloS one* **2013**, 8, (6), e66098.
 47. Wang, D.; Feng, K.; Chen, L.; Zu, S.; Han, S.; Zhu, G., [Relation between fat mass, fat free mass and ventilatory function in children and adolescents]. *Sheng li xue bao:[Acta physiologica Sinica]* **2010**, 62, (5), 455-464.
 48. Joens-Matre, R. R.; Welk, G. J.; Calabro, M. A.; Russell, D. W.; Nicklay, E.; Hensley, L. D., Rural–urban differences in physical activity, physical fitness, and overweight prevalence of children. *The Journal of rural health* **2008**, 24, (1), 49-54.
 49. Özdirenç, M.; Özcan, A.; Akin, F.; Gelecek, N., Physical fitness in rural children compared with urban children in Turkey. *Pediatrics International* **2005**, 47, (1), 26-31.
 50. Micklesfield, L. K.; Pedro, T. M.; Kahn, K.; Kinsman, J.; Pettifor, J. M.; Tollman, S.; Norris, S. A., Physical activity and sedentary behavior among adolescents in rural South Africa: levels, patterns and correlates. *BMC public health* **2014**, 14, (1), 1.
 51. Khalequzzaman, M.; Kamijima, M.; Sakai, K.; Ebara, T.; Hoque, B. A.; Nakajima, T., Indoor air pollution and health of children in biomass fuel-using households of Bangladesh: comparison between urban and rural areas. *Environmental health and preventive medicine* **2011**, 16, (6), 375-383.
 52. Fuel choice, acute respiratory infection and child growth in Uganda. <http://docs.lib.purdue.edu/dissertations/AAI1597565/> (October 5),
 53. Sanbata, H.; Asfaw, A.; Kumie, A., Association of biomass fuel use with acute respiratory infections among under-five children in a slum urban of Addis Ababa, Ethiopia. *BMC public health* **2014**, 14, (1), 1.
 54. Hartley, D., Rural health disparities, population health, and rural culture. *American Journal of Public Health* **2004**, 94, (10), 1675-1678.
 55. Mbonye, A. K., Risk factors for diarrhoea and upper respiratory tract infections among children in a rural area of Uganda. *Journal of Health, Population and Nutrition* **2004**, 52-58.
 56. Uganda Demographic and Health Survey 2011. <http://dhsprogram.com/pubs/pdf/PR18/PR18.pdf> (October 13),
 57. Child Anthropometrics and Malnutrition in Uganda. http://siteresources.worldbank.org/INTSURAGRI/Resources/7420178-1294259038276/UG_Anthro_Brief.pdf (October 13),
 58. Kikafunda, J. K.; Walker, A. F.; Collett, D.; Tumwine, J. K., Risk factors for early childhood malnutrition in Uganda. *Pediatrics* **1998**, 102, (4), e45-e45.
 59. Vella, V.; Tomkins, A.; Borghesi, A.; Migliori, G. B.; Adriko, B.; Crevatin, E., Determinants of child nutrition and mortality in north-west Uganda. *Bulletin of the World Health Organization* **1992**, 70, (5), 637.

CHAPTER 9: GENERAL DISCUSSION

9.1 Summary of main findings

The main objective of this thesis was to determine the prevalence, morbidity and mortality of asthma and associated factors in Uganda. Population-based and hospital-based surveys and prospective cohort studies were conducted to achieve this objective. The main findings on prevalence, morbidity and mortality and factors associated with asthma are summarized below.

Prevalence of asthma in Uganda (Chapter 2): To determine the prevalence of asthma in Uganda, a population-based survey including 3416 participants from all regions of the country was conducted. Participants who reported either wheeze in the last 12 months, history of current use of asthma medications at the time of the survey or history of ever being diagnosed by a physician of asthma were considered to have asthma. We found that the prevalence of asthma was 11.0% (95% CI: 8.9–13.2; males 10.3%, females 11.4%, urban 13.0% and rural 8.9%). By diagnostic criteria, i.e. wheeze in the last 12 months, history of current use of asthma medications at the time of the survey or history of physician diagnosis of asthma, 9.3%, 1.7%, and 0.7% of the participants could be classified as having asthma respectively.

Asthma morbidity and mortality: The morbidity and mortality associated with asthma in Uganda were investigated in three studies in this thesis (**Chapter 3, 4 & 5**). Of the 792 patients who attended the chest clinic in a one-year period, 16.9% were diagnosed with asthma while 2.5% of 16 800 patients who attended the accident and emergency (A&E) in the same period were diagnosed with asthma. Among 568 in patients who were hospitalized in the pulmonology ward over a one-year period, 6.3% were asthmatics. In the prospective cohort of 449 asthma patients followed up for 2 years, we found that the majority of the patients had uncontrolled asthma at baseline (66.8%). A total of 17 patients died during follow up (3.7%, 27.3 deaths per 1000 person years) and 59.6% of the patients experienced at least one exacerbation while 32.4% experienced three or more exacerbations per year (**Chapter 5**). Exacerbations increased with decreased asthma control as measured by the asthma control test (ACT) and increased with increased number of baseline exacerbations. Mortality increased with decreased FEV₁.

Factors associated with asthma: The factors associated with asthma in Uganda are presented in **Chapter 2, 6, 7 & 8**. In chapter 2, a range of factors associated with asthma at population level was explored. The prevalence of asthma was significantly higher among smokers 14.2% than non-smokers 6.3%, $p < 0.001$, those exposed to biomass smoke 28.0% than those not exposed to biomass smoke 20.0%, $p < 0.001$, those with a family history of asthma 26.9% than those without a family history of asthma 9.4%, $p < 0.001$, those with history of TB 3.1% than those without a history of TB 1.30%, $p = 0.01$, with self-reported HIV infection 15.5 % than without HIV 9.1%, $p = 0.025$ and with hypertension 17.9% than without hypertension 12.0%, $p = 0.003$. In multivariate analysis, smoking (adjusted odds ratio (AOR), 3.26; 1.96–5.41, $p < 0.001$), family history of asthma (AOR 2.90; 0.98–4.22 $p < 0.001$), nasal congestion (AOR 3.56; 2.51–5.06, $p < 0.001$), biomass smoke exposure (AOR 2.04; 1.29–3.21, $p = 0.002$) and urban residence (AOR 2.01; 1.23–3.27, $p = 0.005$) were independently associated with asthma.

In **chapter 6, 7 & 8**, the impact of HIV and air pollution were studied. In **chapter 6**, we found that of 2067 participants in the Uganda National asthma survey, 103 (5.0%) were people living with

HIV (PLHIV). Asthma prevalence was 15.5% among PLHIV and 9.1% among those without HIV, prevalence ratio (PR) 1.72, (95%CI 1.07–2.75, $p=0.025$). HIV modified the association of asthma with the following factors, PLHIV vs. not PLHIV: tobacco smoking (12% vs. 8%, $p=<0.001$), biomass use (11% vs. 7%, $p=<0.001$), allergy (17% vs. 11%, $p=<0.001$), family history of asthma (17% vs. 11%, $p=<0.001$), and prior TB treatment (15% vs. 10%, $p=<0.001$). In **chapter 7**, we evaluated the level of air pollution in two cities in Uganda. We found the mean concentration of particulate pollutants with aerodynamic diameter smaller than $2.5\ \mu\text{m}$ ($\text{PM}_{2.5}$) to be $132.1\ \mu\text{g}/\text{m}^3$ which is 5 times the WHO threshold of $25\ \mu\text{g}/\text{m}^3$. In **chapter 8**, we investigated the impact of air pollution on the lung health of children by comparing the lung health and lung function of children in polluted urban areas to that of rural children. Results from this study show that urban children had lower lung function parameters. The proportions of children with $\text{FEV1} < 80\%$ was 12.0% vs. 5.3%, $p = 0.021$ and $\text{FEF}_{25-75} < 80\%$ was 37.7% vs. 29.3%, $p = 0.052$ for urban and rural children respectively.

9.2 Interpretation

Prevalence of asthma: Although a direct comparison of the prevalence of asthma (11.0%) found in Uganda to the global and African regional prevalence previously reported is made quite difficult due to differences in methodologies and case definition of asthma used in the different surveys, it appears to be higher than previously reported.^{1,2,3,4,5} The World health survey conducted by the WHO between 2002–2003, used case definitions almost similar to those used in our asthma prevalence survey.¹ They used 3 definitions: *doctor diagnosed asthma* which was based on the question: “Have you ever been diagnosed with asthma?”. *Clinical asthma* which was based on doctor diagnosed asthma and/or a positive response in either of two questions: “Have you ever been treated for asthma?” or “Have you been taking any medications or treatment for asthma during the last 2 weeks?”. *Symptomatic asthma* was based on the question “During the last 12 months have you experienced attacks of wheezing or whistling breath?”. The average prevalence of asthma in the African region based on these definitions (Table 1) vs. what we found in the Uganda asthma survey based on the same definitions are as follows: doctor diagnosed asthma (3.94% vs. 1.7%), clinical asthma 4.19% vs. 0.7% and symptomatic asthma was 7.75% vs. 9.3%.

Table 9.1: Region and country-specific estimates of asthma prevalence by 3 definitions from To T et al, BMC Public Health, <https://doi.org/10.1186/1471-2458-12-204>.¹

Region ¹	Country	Asthma Prevalence (%) ²		
		Doctor Diagnosed Asthma	Clinical Asthma	Wheezing Symptoms
Africa	Burkina Faso	2.02	2.26	5.32
	Chad	3.68	3.94	7.64
	Comoros ³	7.55	7.80	12.85
	Congo ³	4.65	4.79	7.93
	Cote d'Ivoire ³	4.22	4.59	7.70
	Ethiopia	2.00	2.00	5.53
	Ghana	3.65	3.77	4.88
	Kenya	2.86	3.12	6.22
	Malawi	4.62	4.67	7.76
	Mali	2.65	2.82	4.77
	Mauritania	6.95	7.54	11.78
	Mauritius	3.88	3.92	6.88
	Namibia	3.16	3.39	8.14
	Senegal	3.43	3.72	8.40
	South Africa ⁵	5.92	6.09	12.40
	Swaziland ⁵	8.74	9.69	15.37
	Zambia ⁴	2.83	2.96	6.25
	Zimbabwe	2.28	2.52	5.48
	Regional Sub-total	3.94	4.19	7.75
	World wide	4.27	4.46	8.61

The reasons for the higher prevalence of asthma in Uganda are not clear at this point, but we believe that differences in methodology and case definitions, differences in the time the surveys were conducted and the high prevalence of risk factors for asthma in the country such as indoor and outdoor air pollution, HIV, hypertension and TB could be responsible for the observed differences. Generally, the increasing prevalence of asthma in LMIC has been attributed to various factors notably e.g. urbanization, increasing exposures to environmental risk factors and adoption of westernized affluent lifestyles.^{2, 12}

Morbidity and Mortality: Studies in this thesis have revealed high rates of asthma morbidity and mortality. Asthma patients experience high rates of exacerbations and many of them die from asthma. Up to 59.6% of the patients experienced at least one exacerbation and 32.4% experienced three or more exacerbations in a year which is much higher than seen in other settings.^{13, 14} For example, of the 222,817 and 211,807 patients with asthma in the US and UK asthma databases, respectively, 12.5 and 8.4% experienced ≥ 1 exacerbation during a 12 months follow-up period.¹⁴ Mortality is similarly high, 27.3 per 100 person years compared to 1 per 100 person years reported in some developed settings.¹⁵ In many developed parts of the world the mortality from asthma is decreasing, being estimated at 0.15 per 1000 for the period 2007–2009 in the USA.¹⁶⁻¹⁸

The high rates of asthma morbidity and mortality found in our studies are most likely a reflection of the poor access to health care and appropriate medications as we have shown in studies in this thesis and other studies.^{19, 20} We found that only 32.7% of the patients who participated in the prospective cohort study described in this thesis were using any form of inhaled corticosteroid despite the fact that more than two thirds had uncontrolled asthma. In other studies conducted in Uganda we have found limited availability and affordability of asthma medications and diagnostics.²¹ Another measure of disease morbidity is health care utilization. We found in two hospital studies included in this thesis, low representation of asthma within hospital settings; 16% in the chest clinic, 2.5% in the A&E and 6.3% in the pulmonary ward. This is despite the fact that a high prevalence of asthma was found at population level. Indeed, in the population survey, up to 98% of participants classified as asthmatics were neither aware of their diagnosis nor on any asthma medication. As a comparison, in the USA (2001), asthma accounted for one-quarter of all emergency room visits (in our setting it was only 2.5%), more than 10 million outpatient visits and 500,000 hospitalizations each year. More recently in 2010, about 60% of American asthmatics were hospitalized in a year.^{18, 22} These data show a problem of low awareness of the disease. This is further elaborated by high rates of uncontrolled asthma presented to hospitals, high rates of asthma exacerbations and mortality. We therefore conclude that the high asthma mortality observed in Uganda are due to poor access to the quality of asthma care.

Factors associated with asthma: In this thesis we found many factors traditionally known to be associated with asthma such as family history of asthma, gender, urbanization, allergies and smoking also to be associated with asthma in Uganda. In addition, we found associations of asthma with hitherto not well documented factors such as HIV, TB and exposure to biomass smoke. These factors are highly prevalent in SSA which could make them the biggest drivers of asthma in SSA. The majority of the high TB burden countries are in Africa and 25 million of the 36.7 million people estimated to be infected with HIV are in Africa.^{1, 23} Globally, about 3 billion people (majority from LMIC) depend on biomass fuels for cooking, lighting and heating indoors in poorly ventilated places.²⁴ At the same time it is estimated that 97% of cities in Africa do not meet air quality standards of the WHO.²⁵ While we found biomass smoke to be associated with asthma in studies in this thesis as has been the case in many other studies, some other analyses did not find this association. This may probably be attributed to ubiquitous exposure to biomass smoke in Africa and the framing of the questions to assess exposure.^{26, 27} In our asthma survey, we framed the question as follows “*Does the household cook using biomass fuel (wood, charcoal, etc.) in the living space? (Circle one) 1- Yes 0- No*”.²⁸ Although we did not perform a direct analysis of the association between asthma and ambient air pollution, we did conduct a study that found air pollution to be associated with lung function deficits in children (**Chapter 8**). These deficits in the function of growing lungs in children have been found to predispose the sufferers to wheezing illness as children and asthma and COPD as adults²⁹⁻³². Based on this and previously published literature we contend that ambient air pollution is a key driver of asthma in Uganda.

9.3 Strengths of the studies

Studies in this thesis have strengths that make them suitable for defining the burden of asthma in Africa in general and in Uganda in particular. We conducted one of the largest general population-based surveys to establish the population prevalence of asthma and associated factors. In addition to this survey we also conducted hospital-based surveys to assess the level of health care utilization due to

asthma. These studies have helped us to establish that although the prevalence of asthma at community level is high, many of those with asthma do not access care. This is important for clinical and public health programming. Another strength of our studies is that we assembled a prospective cohort study to investigate the burden of asthma. In this cohort we were able to determine the death rates as well as the causes of death in a prospective manner which strengthens our data on asthma mortality. This study is one of the first asthma mortality cohort studies in SSA. Further to these strengths we extended our understanding of asthma epidemiology by conducting separate studies on key factors that are associated with asthma, namely HIV and air pollution. These studies have expanded our understanding of the importance of these risk factors as far as asthma is concerned.

9.4 Limitations of the studies

Several limitations of the studies in thesis should be noted. The first limitation relates to the definition of asthma in the prevalence survey. We used a questionnaire to define asthma without addition of confirmatory asthma tests. Although this is common practice in many asthma surveys, we appreciate that asthma symptoms could be due to many other differential diagnoses. We however made an effort to address differential diagnoses and conducted spirometry in all participants classified as asthmatics who were 35 years and older to exclude COPD. The addition of spirometry to exclude COPD in older participants is probably one of the first of its kind. The identification of the risk factors for asthma in our studies are limited by the cross-sectional design of the studies which cannot yield any causality data. Another limitation of the studies on morbidity of asthma is that the health care utilization data was generated from hospital records which in many cases could be incomplete, especially in LMIC. Lastly, although we found an association between family history of asthma and asthma we did not conduct genetic epidemiology studies despite the fact that gene-environment interactions are key in asthma causation.

9.5 Overall conclusion

In this thesis, we have shown that asthma is highly prevalent within the Ugandan population. Only few of asthma patients are seen within health care facilities and the majority of asthma patients are undiagnosed and untreated. Access to key medications such as inhaled corticosteroids is very poor. Asthma morbidity is very high as more than two thirds of asthmatics are uncontrolled, more than 50% experience at least one exacerbation in a year and one in three experience more than three exacerbations in a year. Asthma mortality is over twenty times that of the global rate. Asthma in Uganda is associated with factors commonly associated with asthma such as a family history of asthma, allergies and urbanization but factors such as HIV, TB and biomass smoke exposure were also found to be associated with asthma.

9.6 Recommendations

The findings in this thesis have community, clinical, public health, policy and research implications. We make the following recommendations:

Community recommendations

- a) At the community level, we recommend that community awareness campaigns should be undertaken such that the community is aware of the symptoms and signs of asthma as well as asthma risk factors. This will help to create demand for care and diagnostic services within health facilities. Awareness campaigns will

also help to reduce stigma and misconceptions about asthma. Campaigns should emphasize the aetiology of asthma and the fact that it can be treated.

- b) Information education and communication (IEC) materials such as posters need to be displayed within health facilities to alert patients seeking care of the symptoms and signs of asthma for them to request asthma assessment.

Clinical care recommendations

- a) At the clinical level, all primary health care practitioners should be trained regarding asthma diagnosis and management. As reported in Chapter 3, even at the national referral hospital guideline appropriate care was not offered.
- b) For diagnosis of asthma in primary care settings in LMICs, we make the following recommendations. In a patient who presents with respiratory symptoms of cough, wheeze, chest tightness, dyspnea/shortness of breath, health workers should elicit if the symptoms are variable-in relation to time of day and season and if an identifiable trigger can be named by the patient. In patients with any respiratory symptom irrespective of the nature, clinicians need to elicit supportive evidence of asthma namely family history of asthma, allergy, previous response to asthma medications and prior diagnosis of asthma by a physician. Where spirometry is available in the health facility, all patients should undergo reversibility testing for purposes of excluding chronic obstructive pulmonary disease (COPD) only. Peak flow meters may also be used to test diurnal variability if spirometry is not available. All patients presenting with respiratory symptoms in whom COPD is excluded by spirometry and in whom a clinician has no alternative cause for the respiratory symptoms such as TB (negative TB tests) and cardiac disease, asthma treatment should be initiated and followed up in two weeks to assess response to it. In health facilities without spirometry, patients presenting with respiratory symptoms who are 35 years and younger and in who no alternative cause for the respiratory symptoms such as TB (negative TB tests) and cardiac disease, asthma therapy should be initiated and the patient should be followed up in two weeks to assess response to it. Those who are older than 35 years should have asthma therapy initiated and referred for spirometry testing. If after two weeks they have not accessed spirometry and there is no response to asthma therapy, COPD therapy should be added.
- c) For treatment of an asthma exacerbation, we recommended that the government makes *attack packs* containing a short-acting beta agonist (SABA) such as salbutamol and a one-week course of prednisolone. One package should include dosages for adolescents and adults and one for children (bearing a symbol of a child). Four puffs of salbutamol should be used every 4 hours for the first day and thereafter as needed. All patients presenting with acute attacks of breathlessness in whom an alternative diagnosis cause such as pneumonia, TB and cardiac disease have been excluded should receive *attack packs* irrespective of whether the attack is asthma or COPD. Nebulization could be added where available.
- d) Based on findings associating HIV and TB with asthma, we recommend routine screening for asthma in HIV and TB clinics. These patients regularly attend care, yet they are not screened for asthma and other non-communicable diseases.

Figure 9.1 Pathways for clinical diagnosis of asthma in resource limited settings, AFO=Airflow obstruction, COPD=Chronic obstructive pulmonary disease.

Policy recommendations

At the policy level, the Ministry of Health should:

- Facilitate the development and dissemination of national asthma guidelines. This is important because most of the management recommendations in the international guidelines are not available in Uganda and other LMIC.
- We also recommend that essential asthma medications as stipulated by the WHO list be made available in primary care.³³ While a non-communicable diseases (NCDs) department exists within the ministry of

health, we recommend that a special section in this department be created and dedicated to asthma and COPD. In order to attend to the special needs of these diseases since they have a huge interaction with the environment that may not be addressed within all the other NCDs.

- c) Policies and interventions should be made to address indoor and outdoor air pollution. Primary and secondary prevention of these factors should be undertaken. Children and adults, especially women, need to be protected from (early life) exposures to indoor and outdoor air pollution. Simple solutions such as use of clean cookstoves should be rolled out to reduce air pollution indoors. Ordinances and by laws prohibiting rubbish burning in cities and bush burning in rural communities should be enacted and enforced. Education about the sources and dangers of air pollution is key, especially to children in schools. Laws prohibiting importation of old vehicles should be enacted and enforced and roads in the cities should be paved to reduce dust pollution.
- d) For asthma programming at national or regional or district level, we recommend the model shown in Figure 9.2. This model is based on our experience conducting studies in this thesis and clinical practice in Africa. The development of the model is based on the *PRECEDE-PROCEED* planning model.³⁴ The *PRECEDE-PROCEED* planning model is based on theory that behavior change is voluntary and that health programs are likely to be more effective if those to have benefit from them and are affected are involved. The model provides a step by step approach to designing a health program. During the PRECEDE phase, programmers should assess social, epidemiological, behavioral, environmental, educational, and ecological factors related to the program. During the PROCEED phase, pilot-testing and evaluation of the implementation of the strategy, its impact on mediators and outcomes of the population under study is undertaken.

Figure 9.2 Scheme for establishing a national or regional asthma program in resource limited settings.

Research recommendations

In terms of research, we recommend that the scientific community undertakes further biomedical research to understand the detailed mechanisms of the factors associated with asthma. Urgently needed is implementation research to guide on how asthma care can be organized in SSA including innovations of increasing access to asthma medications and diagnostics.

References

1. To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC public health*. 2012;12(1):204.
2. Adeboye D, Chan KY, Rudan I, et al. An estimate of asthma prevalence in Africa: a systematic analysis. *Croatian medical journal*. 2013;54(6):519-531.
3. Institute for Health Metrics and Evaluation online database Available: <http://ghdx.healthdata.org/gbd-results-tool>. Accessed May 22, 2019.
4. Kwizera R, Musaazi J, Meya DB, et al. Burden of fungal asthma in Africa: A systematic review and meta-analysis. *PloS one*. 2019;14(5):e0216568.
5. Obel KB, Ntumba KJM, Kalambayi KP, et al. Prevalence and determinants of asthma in adults in Kinshasa. *PloS one*. 2017;12(5):e0176875.
6. Ehrlich R, White N, Norman R, et al. Wheeze, asthma diagnosis and medication use: a national adult survey in a developing country. *Thorax*. 2005;60(11):895-901.
7. Karahyla JK, Garg K, Garg RK, et al. Tuberculosis and Bronchial Asthma: Not an Uncommon Association. *Chest Journal*. 2010;138(4_MeetingAbstracts):670A-670A.
8. Dogra S, Arden CI, Baker J. The relationship between age of asthma onset and cardiovascular disease in Canadians. *J Asthma*. 2007;44(10):849-854.
9. Yun HD, Knoebel E, Fenta Y, et al. Asthma and Proinflammatory Conditions: A Population-Based Retrospective Matched Cohort Study. *Mayo Clin Proc*. 2012;87(10):953-960.
10. Ferguson S, Teodorescu MC, Gangnon RE, et al. Factors associated with systemic hypertension in asthma. *Lung*. 2014;192(5):675-683.
11. Lunyera J, Kirenga B, Stanifer JW, et al. Geographic differences in the prevalence of hypertension in Uganda: Results of a national epidemiological study. *PloS one*. 2018;13(8):e0201001.
12. Weinberg EG. Urbanization and childhood asthma: an African perspective. *Journal of allergy and clinical immunology*. 2000;105(2):224-231.
13. Griswold SK, Nordstrom CR, Clark S, et al. Asthma exacerbations in North American adults: who are the “frequent fliers” in the emergency department? *Chest*. 2005;127(5):1579-1586.
14. Suruki RY, Daugherty JB, Boudiaf N, et al. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA. *BMC pulmonary medicine*. 2017;17(1):74.
15. De Marco R, Locatelli F, Cazzoletti L, et al. Incidence of asthma and mortality in a cohort of young adults: a 7-year prospective study. *Respiratory research*. 2005;6(1):95.
16. Wijesinghe M, Weatherall M, Perrin K, et al. International trends in asthma mortality rates in the 5-to 34-

- year age group: a call for closer surveillance. *Chest*. 2009;135(4):1045-1049.
17. Moorman JE. National surveillance for asthma--United States, 1980-2004. 2007.
 18. Akinbami LJ, Bailey CM, Johnson CA, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. 2012.
 19. Kirenga BJ, de Jong C, Mugenyi L, et al. Rates of asthma exacerbations and mortality and associated factors in Uganda: a 2-year prospective cohort study. *Thorax*. 2018;73(10):983-985.
 20. Kirenga J, Okot-Nwang M. The proportion of asthma and patterns of asthma medications prescriptions among adult patients in the chest, accident and emergency units of a tertiary health care facility in Uganda. *African health sciences*. 2012;12(1):48-53.
 21. Kibirige D, Kampiire L, Atuhe D, et al. Access to affordable medicines and diagnostic tests for asthma and COPD in sub Saharan Africa: the Ugandan perspective. *BMC pulmonary medicine*. 2017;17(1):179.
 22. New asthma estimates: tracking prevalence, health care, and mortality. Fact Sheet; 2001 Available: <https://www.cdc.gov/nchs/pressroom/01facts/asthma.htm>. Accessed March 11, 2019.
 23. Marais BJ. Childhood tuberculosis: epidemiology and natural history of disease. *The Indian Journal of Pediatrics*. 2011;78(3):321-327.
 24. Household air pollution and health Available: <https://www.who.int/news-room/fact-sheets/detail/household-air-pollution-and-health>. Accessed March 7, 2019.
 25. WHO Global Ambient Air Quality Database (update 2018) Available: <https://www.who.int/airpollution/data/cities/en/>. Accessed March 7, 2019.
 26. Gaviola C, Miele CH, Wise RA, et al. Urbanisation but not biomass fuel smoke exposure is associated with asthma prevalence in four resource-limited settings. *Thorax*. 2016;71(2):154-160.
 27. Trevor J, Antony V, Jindal SK. The effect of biomass fuel exposure on the prevalence of asthma in adults in India--review of current evidence. *Journal of Asthma*. 2014;51(2):136-141.
 28. van Gemert F, Kirenga B, Chavannes N, et al. Prevalence of chronic obstructive pulmonary disease and associated risk factors in Uganda (FRESH AIR Uganda): a prospective cross-sectional observational study. *The Lancet Global Health*. 2015;3(1):e44-e51.
 29. Gray D, Willemse L, Visagie A, et al. Determinants of early-life lung function in African infants. *Thorax*. 2016;thoraxjnl-2015-207401.
 30. Martinez FD. The origins of asthma and chronic obstructive pulmonary disease in early life. *Proceedings of the American Thoracic Society*. 2009;6(3):272-277.
 31. Bui DS, Burgess JA, Lowe AJ, et al. Childhood Lung Function Predicts Adult Chronic Obstructive Pulmonary Disease and Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome. *Am J Respir Crit Care Med*. 2017;196(1):39-46.
 32. Stern DA, Morgan WJ, Wright AL, et al. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet*. 2007;370(9589):758-764.
 33. World Health Organisation Model list of Essential Medicines 2017 Available: <https://apps.who.int/iris/bitstream/handle/10665/273826/EML-20-eng.pdf?ua=1>. Accessed March 12, 2019.
 34. Green LW, Kreuter MW. Health promotion planning: An educational and ecological approach: Mayfield publishing company Mountain View, CA 1999.

CHAPTER 10: SUMMARY

Asthma is defined by the Global Initiative for Asthma (GINA) as a heterogenous disease usually characterized by chronic airway inflammation and accompanied by history of recurrent or persistent respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable airflow obstruction. It is estimated that asthma currently affects 334 million people globally and 420,000 people died of asthma worldwide in the year 2016.

The prevalence of asthma is decreasing in most developed western countries, but is reported to be increasing in most low- and middle-income countries (LMIC) especially those in Africa where its numbers have increased from an estimated 74.4 million in 1990 to 119.3 million in 2010. The increasing prevalence of asthma in LMIC has been attributed to various factors including urbanization, increasing exposure to environmental risk factors and adoption of westernized affluent lifestyles.

In Sub Saharan Africa (SSA), recent population-based asthma prevalence data and prospectively collected asthma morbidity and mortality data is lacking. This has created a situation of low awareness of the disease, and limited availability of medicines, diagnostic tests and skilled personnel for asthma management. To fill this data gap, the studies in this thesis determined the prevalence, morbidity and mortality of asthma and associated factors in SSA, using Uganda as a case study.

Following a general introduction about asthma definition, burden, pathology, risk factors and treatment (**chapter 1**), the first research study of this thesis (**chapter 2**) is presented. The data in this study was collected in a population-based survey of 3416 adolescents and adult participants from five regions of Uganda including the capital city, Kampala. The prevalence of asthma obtained in this study was 11.0%. Notably, this was higher than the global average of 8.8% and the African average of 7.8% found in the world health survey. The prevalence of asthma was significantly higher among smokers 14.2% than non-smokers 6.3%, $p < 0.001$, those exposed to biomass smoke 28.0% than those not exposed to biomass smoke 20.0%, $p < 0.001$, those with a family history of asthma 26.9% than those without a family history of asthma 9.4%, $p < 0.001$, those with history of TB 3.1% than those without a history of TB 1.30%, $p = 0.01$, with self-reported HIV infection 15.5 % than without HIV 9.1%, $p = 0.025$ and with hypertension 17.9% than without hypertension 12.0%, $p = 0.003$. In multivariate analysis smoking, (adjusted odds ratio (AOR), 3.26 (1.96–5.41, $p < 0.001$) family history of asthma, AOR 2.90 (98–4.22 $p < 0.001$), nasal congestion, AOR 3.56 (2.51–5.06, $p < 0.001$), biomass smoke exposure, AOR 2.04 (1.29–3.21, $p = 0.002$) and urban residence, AOR 2.01 (1.23–3.27, $p = 0.005$) were independently associated with asthma. Up to 98% of those with asthma did not know they had asthma and were not receiving any form of treatment.

Chapter 3 and 4 present the prevalence of asthma in hospital settings in Kampala, Uganda. Of the 792 patients who attended the Mulago Hospital chest clinic in a one-year period, only 16.9% were diagnosed with asthma. In addition, only 2.5% of the 16 800 patients who attended the emergency department of the same hospital during the same period were diagnosed with asthma. In the pulmonology ward of the same hospital, 6.3% of the 568 patients over a one-year period were asthmatics. These relatively low rates of asthmatics in daily care are remarkable given the fact that the prevalence survey (**chapter 2**) found a high prevalence of untreated asthma in the population. The rates are also much lower than those in respiratory departments in developed countries. This low representation of asthma in routine care is

probably due to lack of awareness of asthma among patients. It could also be due to lack asthma care in health facilities which make patients to have poor health care seeking behavior.

In **chapter 5**, findings from a 2-year prospective cohort study of 449 asthma patients in Uganda are presented. In this study, it was found that the majority (66.8%) of the patients had uncontrolled asthma at baseline. A total of 17 patients died during follow up (3.7%, 27.3 deaths per 1000 person years) and 32.4% of the patients experienced three or more exacerbations per year. Exacerbations increased with increasing number of baseline exacerbations. Mortality increased with decreasing FEV₁. Of note, only 32.7% of asthma patients were using inhaled corticosteroids at baseline and the proportion dropped to 12.9% at month 24 with main reason for discontinuing therapy being cost of the medication.

Chapter 6 presents results of the analysis for the impact of HIV on the prevalence of asthma. As can be seen in this chapter, HIV is a significant driver of asthma in Uganda. Among 2067 participants who knew their HIV status, 103 (5.0%) were people living with HIV (PLHIV). Asthma prevalence was 15.5% among PLHIV and 9.1% among those without HIV, resulting in a prevalence ratio (PR) of 1.72, $p=0.025$. HIV modified the association of asthma with other asthma risk factors: PLHIV vs. not PLHIV: tobacco smoking (12% vs. 8%, $p<0.001$), biomass use (11% vs. 7%, $p<0.001$), allergy (17% vs. 11%, $p<0.001$), family history of asthma (17% vs. 11%, $p<0.001$), and prior TB treatment (15% vs. 10%, $p<0.001$).

In **chapter 7 and 8**, we evaluated the levels of air pollution in two cities in Uganda and its impact on asthma. In the air pollution survey, we found the mean concentration of particulate matter with aerodynamic diameter smaller than 2.5 μm (PM_{2.5}) to be 132.1 $\mu\text{g}/\text{m}^3$. Of note, this is 5 times the WHO threshold of 25 $\mu\text{g}/\text{m}^3$. We then compared the lung health and lung function of children living in high ambient air pollution urban areas to those of children living in low ambient air pollution rural areas. Results from this study showed that urban children had lower lung function parameters. The proportion of children with FEV₁ < 80% was 12.0% in polluted areas vs. 5.3% in less polluted areas, $p=0.021$ and FEF_{25–75} < 80% was 37.7% in polluted vs. 29.3% in less polluted areas, $p=0.052$.

We conclude that while asthma is highly prevalent within the Ugandan population, only few asthma patients are seen within health care facilities and the majority of asthma patients are undiagnosed and untreated. Asthma in Uganda is associated with factors well-known to be associated with asthma, such as a family history of asthma, allergies and urbanization. Yet, asthma was also associated with more specific local factors such as HIV, TB and biomass smoke exposure. Access to key medications, such as inhaled corticosteroids, is very low. Asthma morbidity is very high as more than two thirds of asthmatics are uncontrolled and one-in-three experience more than three exacerbations in a year. Asthma mortality is over twenty times the global rate. We recommend primary prevention measures targeting air pollution, biomass smoke exposure and HIV and TB control. We also recommend training of health workers in asthma care, community awareness campaigns and increased access to asthma medications. Finally, we presented two algorithms that can be used to diagnose asthma and to set up programs at national and regional levels in resource-poor settings of Africa. Further research is needed on the detailed mechanisms of asthma causation by the factors associated with asthma as well as implementation research to guide on how asthma care can be organized in SSA including innovations of increasing access to asthma medications and diagnostics.

ACKNOWLEDGEMENTS

The research work presented in this thesis involved many people and many institutions in different parts of the world. All these people and institutions are highly appreciated especially those persons that are co-authors on the different publications in this thesis. I thank the participants of the different research projects in this thesis without whose participation this thesis would not have been written. I also thank the research assistants and data managers and statisticians who meticulously followed the research protocols to ensure that usable data was collected. I thank administrators and finance officers who facilitated the studies in their different capacities.

I would like to acknowledge the support of the different organizations that funded the different research projects in this thesis; GSK's Trust in Science Africa project, NIH (Award No. R24 TW008861) and Noordelijke cara stichting (NCS), The Netherlands and the International Primary Care Respiratory Group (IPCRG). Special thanks go to MakCHS – UC Berkeley- Yale Pulmonary Complications of AIDS Research Training (PART) Program, NIH D43TW009607, from the Fogarty International Center for funding the writing and printing of this thesis. I also highly appreciate the support from the Department of General Practice and Elderly Care Medicine, UMCG, University of Groningen for hosting this PhD. The support from my employer institution, Makerere University and Mulago National Referral Hospital where the clinical studies were conducted is appreciated as well.

I thank my supervisors and advisors; Dr. Corina de Jong, prof. Thys van der Molen, prof. Moses Kamya, and prof. Marike Boezen for their invaluable support during the design, conduct, analysis and publication of the studies in this thesis and the writing of this thesis. Special thanks go to prof. Moses Kamya who introduced me to the FRESH AIR research group through which I was able to access the vital mentorship from professors at the UMCG who have supervised me in this PhD programme. The FRESH AIR group has not only expanded research in Uganda but it has contributed to capacity building for respiratory medicine including supporting the founding of the Makerere University Lung Institute.

To my colleagues, Frederik van Gemert, Rupert Jones, Job van Boven and those at the Makerere University Lung Institute and the Department of Medicine, Makerere University and the University of Groningen, I am very grateful for your contributions to the work in this thesis; the brainstorming on research ideas, the reviews of the manuscripts and thesis and the encouragement that you gave me while undertaking this PhD programme.

I thank my siblings and other relatives especially my brother Cedric for sharing into the responsibility of supporting our extended families. Without this support I would probably have not got the time to complete this PhD programme.

Last but not least to my dear wife and children, your support, endurance and understanding while I was away conducting the studies and writing them up and out of the country on this PhD programme is much appreciated.

May the God almighty reward all of you who helped me with this work whether mentioned by name or not.

CURRICULUM VITAE

Bruce J Kirenga was born in Kiboga district, Uganda on the 12 January 1975 to Mr. Matiya Kakwerere (RIP) and Mrs. Erina M Kakwerere (RIP). He attended Kasega primary school, Bamusuuta secondary school and Makerere College school. He joined Makerere University in 1997 to study medicine. In 2002 he graduated with an MBChB degree. He undertook internship training at Mulago National referral hospital for one year, practiced as general medical officer at The AIDS Support Organisation (TASO) in Entebbe and Kisubi Hospital for two years before moving to work as research medical officer in the TB ward at Mulago Hospital in 2004. In 2006 he enrolled for the Master of Medicine (Internal Medicine, MMed) programme at Makerere University. During the same period, he undertook a 2-year Masters research fellowship of the Royal Tropical Institute, University of Amsterdam offered at the University of Rwanda.

Upon completion of the MMed programme he worked as a specialty Registrar in the Pulmonology Unit of the Department of Medicine of Mulago Hospital. In 2012 he was appointed a Lecturer in the Department of Medicine Makerere University where he still works to date. In 2013-2014 he undertook a 1-year training in pulmonary medicine in the Section of Pulmonary Medicine and Critical Care, Department of Medicine of Yale University School of Medicine. In 2015 he founded the Makerere University Lung Institute and became its founding Director, a position he holds to date.

In June 2015 Bruce enrolled for a PhD programme in the Department of General Practice and Elderly Care Medicine, UMCG, University of Groningen to study asthma epidemiology in Africa.

LIST OF PUBLICATIONS

Asthma/COPD and Related

1. Kwizera R, Musaazi J, Meya DB, Worodria W, Bwanga F, Kajumbula H, Fowler SJ, **Kirenga BJ**, Gore R, Denning DW. Burden of fungal asthma in Africa: A systematic review and meta-analysis. PLOS ONE. 2019 May 16;14(5):e0216568.
2. Siddharthan, T., Grigsby, M., Morgan, B., Kalyesubula, R., Wise, R. A., **Kirenga, B.**, & Checkley, W. (2019). Prevalence of chronic respiratory disease in urban and rural Uganda. *Bulletin of the World Health Organization*, 97(5).
3. Kibirige D, Sanya RE, Nantanda R, Worodria W, **Kirenga B**. Availability and affordability of medicines and diagnostic tests recommended for management of asthma and chronic obstructive pulmonary disease in sub-Saharan Africa: a systematic review. *Allergy, Asthma & Clinical Immunology*. 2019 Dec;15(1):14.
4. **Kirenga B**, Nantanda R, de Jong C, Mugenyi L, Meng Q, Aniku G, Williams S, Aanyu-Tukamuhebwa H, Kamya M, Schwander S, van der Molen T. Lung Function of Children at Three Sites of Varying Ambient Air Pollution Levels in Uganda: A Cross Sectional Comparative Study. *International journal of*
5. **Kirenga BJ**, de Jong C, Katagira W, Kasozi S, Mugenyi L, Boezen M, van der Molen T, Kamya MR. Prevalence and factors associated with asthma among adolescents and adults in Uganda: a general population-based survey. *BMC public health*. 2019 Dec;19(1):227.
6. Robertson NM, Nagourney EM, Pollard SL, Siddharthan T, Kalyesubula R, Surkan PJ, Hurst JR, Checkley W, **Kirenga BJ**. Urban-Rural Disparities in Chronic Obstructive Pulmonary Disease Management and Access in Uganda. *Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation*. 2019;6(1):17.
7. Grigsby MR, Siddharthan T, Pollard SL, Chowdhury M, Rubinstein A, Miranda JJ, Bernabe-Ortiz A, Alam D, **Kirenga B**, Jones R, van Gemert F. Low Body Mass Index Is Associated with Higher Odds of COPD and Lower Lung Function in Low-and Middle-Income Countries. *COPD: Journal of Chronic Obstructive Pulmonary Disease*. 2019 Apr 24:1-8.
8. **Kirenga BJ**, Mugenyi L, de Jong C, Davis JL, Katagira W, van der Molen T, Kamya MR, Boezen M. The impact of HIV on the prevalence of asthma in Uganda: a general population survey. *Respiratory research*. 2018 Dec;19(1):184.
9. Morgan BW, Grigsby MR, Siddharthan T, Kalyesubula R, Wise RA, Hurst JR, **Kirenga B**, Checkley W. Validation of the Saint George's Respiratory Questionnaire in Uganda. *BMJ open respiratory research*. 2018 Jul 1;5(1): e000276.
10. **Kirenga BJ**, Mugenyi L, de Jong C, Davis JL, Katagira W, van der Molen T, Kamya MR, Boezen M. The impact of HIV on the prevalence of asthma in Uganda: a general population survey. *Respiratory research*. 2018 Dec;19(1):184.
11. Siddharthan T, Pollard SL, Quaderi SA, Mirelman AJ, Cárdenas MK, **Kirenga B**, Rykiel NA, Miranda JJ, Shrestha L, Chandyo RK, Cattamanchi A. Effectiveness-implementation of COPD case finding and self-management action plans in low-and middle-income countries: global excellence in COPD outcomes (GECoc) study protocol. *Trials*. 2018 Dec;19(1):571.
12. Katoto P, Murhula A, Kayembe-Kitenge T, Lawin H, Bisimwa B, Cirhambiza J, Musafiri E, Birembano

- F, Kashongwe Z, **Kirenga B**, Mfinanga S. Household Air Pollution Is Associated with Chronic Cough but Not Hemoptysis after Completion of Pulmonary Tuberculosis Treatment in Adults, Rural Eastern Democratic Republic of Congo. *International journal of environmental research and public health*. 2018 Nov 15;15(11):2563.
13. van Kampen SC, Jones R, Kitembo H, Houben RM, Wei Y, Mugabe FR, Rutebemberwa E, **Kirenga B**. Chronic respiratory symptoms and lung abnormalities among people with a history of tuberculosis in Uganda: a national survey. *Clinical infectious diseases*. 2018 Sep 18.
 14. Jones R, Muyinda H, Nyakoojo G, **Kirenga B**, Katagira W, Pooler J. Does pulmonary rehabilitation alter patients' experiences of living with chronic respiratory disease? a qualitative study. *International journal of chronic obstructive pulmonary disease*. 2018; 13:2375.
 15. van Kampen SC, Wanner A, Edwards M, Harries AD, **Kirenga BJ**, Chakaya J, Jones R. International research and guidelines on post-tuberculosis chronic lung disorders: a systematic scoping review. *BMJ global health*. 2018 Jul 1;3(4): e000745.
 16. van Gemert FA, Kirenga BJ, Gebremariam TH, Nyale G, de Jong C, van der Molen T. The complications of treating chronic obstructive pulmonary disease in low income countries of sub-Saharan Africa. *Expert review of respiratory medicine*. 2018 Mar 4;12(3):227-37.
 17. **Kirenga BJ**, de Jong C, Mugenyi L, Katagira W, Muhofa A, Kanya MR, Boezen HM, van der Molen T. Rates of asthma exacerbations and mortality and associated factors in Uganda: a 2-year prospective cohort study. *Thorax*. 2018 May 10: thoraxjnl-2017.
 18. van Gemert FA, **Kirenga BJ**, Gebremariam TH, Nyale G, de Jong C, van der Molen T. The complications of treating chronic obstructive pulmonary disease in low income countries of sub-Saharan Africa. *Expert review of respiratory medicine*. 2018 Mar 4(just-accepted).
 19. Siddharthan T, Grigsby MR, Goodman D, Chowdhury M, Rubenstein A, Irazola V, Gutierrez L, Miranda JJ, Bernabe-Ortiz A, Alam D, **Kirenga B**. Association Between Household Air Pollution Exposure and Chronic Obstructive Pulmonary Disease Outcomes in 13 Low-and Middle-income Country Settings. *American journal of respiratory and critical care medicine*. 2018 Jan 11(ja).
 20. Kibirige D, Kampiire L, Atuhe D, Mwebaze R, Katagira W, Muttamba W, Nantanda R, Worodria W, **Kirenga B**. Access to affordable medicines and diagnostic tests for asthma and COPD in sub Saharan Africa: the Ugandan perspective. *BMC pulmonary medicine*. 2017 Dec;17(1):179.
 21. Jones R, **Kirenga BJ**, Katagira W, Singh SJ, Pooler J, Okwera A, Kasiita R, Enki DG, Creanor S, Barton A. a pre–post intervention study of pulmonary rehabilitation for adults with post-tuberculosis lung disease in Uganda. *International journal of chronic obstructive pulmonary disease*. 2017; 12:3533.
 22. Morgan BW, Siddharthan T, Grigsby MR, Pollard SL, Kalyesubula R, Wise RA, Kirenga B, Checkley W. Asthma and Allergic Disorders in Uganda: A Population-Based Study Across Urban and Rural Settings. *The Journal of Allergy and Clinical Immunology: In Practice*. 2018 Jan 17.
 23. Siddharthan T, Grigsby MR, Goodman D, Chowdhury M, Rubenstein A, Irazola V, Gutierrez L, Miranda JJ, Bernabe-Ortiz A, Alam D, **Kirenga B**. Association Between Household Air Pollution Exposure and Chronic Obstructive Pulmonary Disease Outcomes in 13 Low-and Middle-income Country Settings. *American journal of respiratory and critical care medicine*. 2018 Jan 11(ja).
 24. van Schayck OC, Williams S, Barchilon V, Baxter N, Jawad M, Katsaounou PA, **Kirenga BJ**, Panaitescu

- C, Tsiligianni KW, Zwar N, Ostrem A. Treating tobacco dependence: guidance for primary care on life-saving interventions. Position statement of the IPCRG. *npj Primary Care Respiratory Medicine*. 2017;27.
25. **Kirenga BJ**, Schwartz JI, de Jong C, van der Molen T, Okot-Nwang M. Guidance on the diagnosis and management of asthma among adults in resource limited settings. *African Health Sciences*. 2015;15(4):1189-99.
 26. **Kirenga BJ**, Jones R, Muhofa A, Nyakoojo G, Williams S. Rapid assessment of the demand and supply of tobacco dependence pharmacotherapy in Uganda. *Public health action*. 2016 Mar 21;6(1):35-7.
 27. **Bruce Kirenga**, Nelson K Sewankambo, Frederik van Gemert, Job va Boven, and Thys van der Molen. Increasing research capacity and awareness of chronic lung diseases in east africa. *The lancet global health blogs*. [cited 2019 May 27]. Available from: <https://www.thelancet.com/journals/langlo/blog>
 28. Gemert FV, Kirenga B, Jones R. The significance of early-life prevention of COPD in sub-Saharan Africa: findings from the FRESH AIR UGANDA survey. *News and Notes*. 2016 Mar;11(2):4.
 29. **Kirenga BJ**, Qingyu M, Frederik van Gemert, Hellen Aanyu-Tukamuhebwa, Niels Chavannes, Achilles Katamba, Gerald Obai, Thys van der Molen, Stephan Schwander, and Vahid Mohsenin. "The State of Ambient Air Quality in Two Ugandan Cities: A Pilot Cross-Sectional Spatial Assessment." *International Journal of Environmental Research and Public Health* 12, no. 7 (2015): 8075-8091.
 30. Molen T, and **Kirenga B**. "COPD: early diagnosis and treatment to slow disease progression." *International journal of clinical practice* 69, no. 5 (2015): 513-514.
 31. van Gemert, F., **Kirenga, B.**, Chavannes, N., Kanya, M., Luzige, S., Musinguzi, P., ... & de Jong, C. (2015). Prevalence of chronic obstructive pulmonary disease and associated risk factors in Uganda (FRESH AIR Uganda): a prospective cross-sectional observational study. *The Lancet Global Health*, 3(1), e44-e51.
 32. Van Gemert, F., Chavannes, N., Nabadda, N., Luzige, S., **Kirenga, B.**, Eggermont, C., ... & van der Molen, T. (2013). Impact of chronic respiratory symptoms in a rural area of sub-Saharan Africa: an in-depth qualitative study in the Masindi district of Uganda. *Primary Care Respiratory Journal*, 22(3), 300-305.
 33. Serugendo, A. N., **Kirenga, B. J.**, Hawkes, M., Nakiyingi, L., Worodria, W., & Okot-Nwang, M. (2014). Evaluation of asthma control using Global Initiative for Asthma criteria and the Asthma Control Test in Uganda. *The International Journal of Tuberculosis and Lung Disease*, 18(3), 371-376.
 34. Kaplan A, Gruffydd-Jones K, van Gemert F, Kirenga BJ, Medford AR. A woman with breathlessness: a practical approach to diagnosis and management. *Primary Care Respiratory Journal*. 2013 Nov 23;22(4):468.
 35. **Kirenga, J. B.**, & Okot-Nwang, M. (2012). The proportion of asthma and patterns of asthma medications prescriptions among adult patients in the chest, accident and emergency units of a tertiary health care facility in Uganda. *African health sciences*, 12(1), 48-53.
 36. Sanya, R. E., **Kirenga, B. J.**, Worodria, W., & Okot-Nwang, M. (2014). Risk factors for asthma exacerbation in patients presenting to an emergency unit of a national referral hospital in Kampala, Uganda. *African health sciences*, 14(3), 707-715.
 37. **B J Kirenga**, L Nakiyingi, W Worodria and M Okot-Nwang: **Chronic respiratory diseases in a tertiary healthcare facility in Uganda**. *African Journal of Respiratory Medicine*. Vol 8 No 2 March 2013
 38. Cragg L, Williams S, Chavannes NH. FRESH AIR: an implementation research project funded through Horizon 2020 exploring the prevention, diagnosis and treatment of chronic respiratory diseases in low-

resource settings. NPJ primary care respiratory medicine. 2016 Jun 30; 26:16035.

39. Brakema EA, van Gemert FA, van der Kleij RM, Salvi S, Puhan M, Chavannes NH. COPD's early origins in low-and-middle income countries: what are the implications of a false start? npj Primary Care Respiratory Medicine. 2019 Mar 5;29(1):6.

TB

40. Najjingo I, Muttamba W, **Kirenga BJ**, Nalunjogi J, Bakesiima R, Olweny F, Lusiba P, Katamba A, Joloba M, Ssengooba W. Comparison of GeneXpert cycle threshold values with smear microscopy and culture as a measure of mycobacterial burden in five regional referral hospitals of Uganda-A cross-sectional study. PloS one. 2019 May 15;14(5):e0216901.
41. Muttamba W, **Kirenga B**, Ssengooba W, Sekibira R, Katamba A, Joloba ML. Prevalence of Tuberculosis Risk Factors among Bacteriologically Negative and Bacteriologically Confirmed Tuberculosis Patients from Five Regional Referral Hospitals in Uganda. The American journal of tropical medicine and hygiene. 2018 Dec 26; tpm180281.
42. Muttamba W, Ssengooba W, Sekibira R, **Kirenga B**, Katamba A, Joloba M. Accuracy of different Xpert MTB/Rif implementation strategies in programmatic settings at the regional referral hospitals in Uganda: Evidence for country wide roll out. PloS one. 2018 Mar 22;13(3): e0194741.
43. Colleen Scott, Simon Walusimbi, **Bruce Kirenga**, Moses Joloba, et al. Evaluation of Automated Molecular Testing Rollout for Tuberculosis Diagnosis Using Routinely Collected Surveillance Data — Uganda, 2012–2015. Scott C. MMWR. Morbidity and Mortality Weekly Report. 2017;66.
44. Ssengooba W, **Kirenga B**, Muwonge C, Kyaligonza S, Kasozi S, Mugabe F, Boeree M, Joloba M, Okwera A. Patient satisfaction with TB care clinical consultations in Kampala: a cross sectional study. African Health Sciences. 2016;16(4):1101-8.
45. Nakaggwa P, Odeke R, **Kirenga BJ**, Bloss E. Incomplete sputum smear microscopy monitoring among smear-positive tuberculosis patients in Uganda. The International Journal of Tuberculosis and Lung Disease. 2016 May 1;20(5):594-9.
46. **Kirenga, B. J.**, Ssengooba, W., Muwonge, C., Nakiyingi, L., Kyaligonza, S., Kasozi, S., ... & Okwera, A. (2015). Tuberculosis risk factors among tuberculosis patients in Kampala, Uganda: implications for tuberculosis control. *BMC public health*, 15(1), 1.
47. Bulage L, Imoko J, **Kirenga BJ**, Lo T, Byabajungu H, Musisi K, Joloba M, Bloss E. Quality of Sputum Specimen Samples Submitted for Culture and Drug Susceptibility Testing at the National Tuberculosis Reference Laboratory-Uganda, July-October 2013. Journal of Tuberculosis Research. 2015 Aug 14;3(03):97.
48. **Kirenga, B. J.**, Ssengooba, W., Muwonge, C., Nakiyingi, L., Kyaligonza, S., Kasozi, S., ... & Okwera, A. (2015). Tuberculosis risk factors among tuberculosis patients in Kampala, Uganda: implications for tuberculosis control. *BMC public health*, 15(1), 1.
49. Mfinanga, S. G., **Kirenga, B. J.**, Chanda, D. M., Mutayoba, B., Mthiyane, T., Yimer, G., ... & Massaga, J. (2014). Early versus delayed initiation of highly active antiretroviral therapy for HIV-positive adults with newly diagnosed pulmonary tuberculosis (TB-HAART): a prospective, international, randomised, placebo-controlled trial. *The Lancet infectious diseases*, 14(7), 563-571.
50. Lusiba, J. K., Nakiyingi, L., **Kirenga, B. J.**, Kiragga, A., Lukande, R., Nsereko, M., ... & Mayanja-

- Kizza, H. (2014). Evaluation of Cepheid's Xpert MTB/Rif test on pleural fluid in the diagnosis of pleural tuberculosis in a high prevalence HIV/TB setting. *PloS one*, 9(7), e102702.
51. **Kirenga, B. J.**, Levin, J., Ayakaka, I., Worodria, W., Reilly, N., Mumbowa, F., ... & Joloba, M. (2014). Treatment outcomes of new tuberculosis patients hospitalized in Kampala, Uganda: a prospective cohort study. *PloS one*, 9(3), e90614.
 52. Mayosi BM, Ntsekhe M, Bosch J, Pandie S, Jung H, Gumedze F, Pogue J, Thabane L, Smieja M, Francis V, Joldersma L. Prednisolone and Mycobacterium indicus pranii in tuberculous pericarditis. *New England Journal of Medicine*. 2014 Sep 18;371(12):1121-30.
 53. Clark TG, Mallard K, Coll F, Preston M, Assefa S, Harris D, Ogwang S, Mumbowa F, **Kirenga B**, O'Sullivan DM, Okwera A. Elucidating emergence and transmission of multidrug-resistant tuberculosis in treatment experienced patients by whole genome sequencing. *PLoS One*. 2013 Dec 11;8(12): e83012.
 54. **B. J. Kirenga**, W. Worodria, M. Massinga-Loembe, T. Nalwoga, Y. C. Manabe, L. Kestens, R. Colebunders, H. Mayanja-Kizza. Tuberculin skin test conversion among HIV patients on antiretroviral treatment in Uganda. **2013** *Int J Tuberc Lung Dis* 17(3):336–341
 55. Nakiyingi, L., Ssengooba, W., Nakanjako, D., Armstrong, D., Holshouser, M., Kirenga, B. J., ... & Manabe, Y. C. (2015). Predictors and outcomes of mycobacteremia among HIV-infected smear-negative presumptive tuberculosis patients in Uganda. *BMC Infectious Diseases*, 15(1), 62.
 56. Fennelly KP, Jones-Lopez EC, Ayakaka I, Kim S, Menyha H, **Kirenga B**, et al. Variability of Infectious Aerosols Produced During Coughing by Patients with Pulmonary Tuberculosis. *American journal of respiratory and critical care medicine*. **2012**. Epub 2012/07/17
 57. Bongani M Mayosi, Mpiko Ntsekhe, Bosch J, Pogue J, Gumedze F, Badri M, Jung, H, Pandie S, Smieja M, Thabane L, Veronica Francis, Kandithal M Thomas, Baby Thomas, Abolade A Awotedu, Nombulelo P Magula, Datshana P Naidoo, Albertino Damasceno, Alfred Chitsa Banda, Arthur Mutyaba, Basil Brown, Patrick Ntuli, Phindile Mntla, Lucas Ntyintyane, Rohan Ramjee, Pravin Manga, MBChB, **Bruce Kirenga**, Charles Mondo, James BW Russell, Jacob M Tsitsi, Ferande Peters, Mohammed R Essop, Ayub Felix Barasa, Mahmoud Sani, Taiwo Olunuga, Okechukwu Ogah, Akinyemi Aje, Victor Ansa, Dike Ojji, Solomon Danbauchi, James Hakim, Jonathan Matenga, Salim Yusuf. Rationale and design of the *Investigation of the Management of Pericarditis (IMPI)* trial: a 2X2 factorial randomized double blind multicentre trial of adjunctive prednisolone and *Mycobacterium w* immunotherapy in tuberculous pericarditis. *American Heart Journal*, available online 13 December **2012**
 58. C. Wekesa, **B. J. Kirenga**, M. L. Joloba, F. Bwanga, A. Katamba, M. R. Kanya. Chest X-ray vs. Xpert® MTB/RIF assay for the diagnosis of sputum smear-negative tuberculosis in Uganda. **2014** *INT J TUBERC LUNG DIS* 18(2):216–219
 59. Graeme Meintjes, Stephen D Lawn, Fabio Scano, Gary Maartens, Martyn A French, William Worodria, Julian H Elliott, David Murdoch, Robert J Wilkinson, Catherine Seyler, Laurence John, Maarten Schim van der Loeff, Peter Reiss, Lut Lynen, Edward N Janoff, Charles Gilks, and Robert Colebunders [on behalf of for the International Network for the Study of HIV-associated IRIS]: Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis*. **2008** August; 8(8): 516–523.
 60. **Bruce J Kirenga**, Duncan M Chanda, Catherine M Muwonge, Getnet Yimer, Francis E Adatu, and Philip C Onyebujoh: Advances in the diagnosis, treatment and control of HIV associated tuberculosis. *African*

OTHERS

61. Lunyera J, **Kirenga B**, Stanifer JW, Kasozi S, van der Molen T, Katagira W, Kamyra MR, Kalyesubula R. Geographic differences in the prevalence of hypertension in Uganda: Results of a national epidemiological study. *PloS one*. 2018 Aug 1;13(8): e0201001
62. JF van Boven, PL An, **BJ Kirenga**, NH Chavannes. Electric scooters: batteries in the battle against ambient air pollution? *The Lancet Planetary Health* 2017; 1(5):e168-169
63. Kalyesubula, Robert, Joseph Lunyera, Gyavira Makanga, **Bruce Kirenga**, and Timothy K. Amukele. "A 4-year survey of the spectrum of renal disease at a National Referral Hospital Outpatient Clinic in Uganda." *Kidney international* 87, no. 3 (2015): 663-663.
64. Viray MA, Wamala J, Fagan R, Luquez C, Maslanka S, Downing R, Biggerstaff M, Malimbo M, **Kirenga JB**, Nakibuuka J *et al*: Outbreak of type A foodborne botulism at a boarding school, Uganda, 2008. *Epidemiol Infect* 2014, 27:1-5.
65. Sethi AK, Acher CW, **Kirenga B**, Mead S, Donskey CJ, Katamba A. Infection Control Knowledge, Attitudes, and Practices among Healthcare Workers at Mulago Hospital, Kampala, Uganda. *Infection control and hospital epidemiology: the official journal of the Society of Hospital Epidemiologists of America*. 2012;33(9):917-23. Epub 2012/08/08
66. **Bruce J Kirenga**, Peter JM Kaddu, Alex Mugume, Margaret Nankya, Lydia Nakiyingi, Mathias Luwemba, Robert Asaba and Samson Kironde. Prevalence of cross generational sex and its association with Human Immunodeficiency Virus infection among tertiary institutions students in a suburban district in Uganda. *UMJ* (2012) 1(1)