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 Jong[3], Levicatus Mugenyi[1,4], Winceslaus Katagira[2], Abdallah Muhofa[2], Moses R Kamya[1], Marike Boezen[5], Thys van der Molen[3]

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**

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 ≥ 12% (and ≥ 200ml) after administration of 400µg of salbutamol) are excluded and registered as having COPD.

Patients who are referred for registration as having COPD but show 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 (ACT[1]). Patients are followed up every six months, at 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 ACT[1]

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 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

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) guidelines[7]) 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 FEV_1) 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

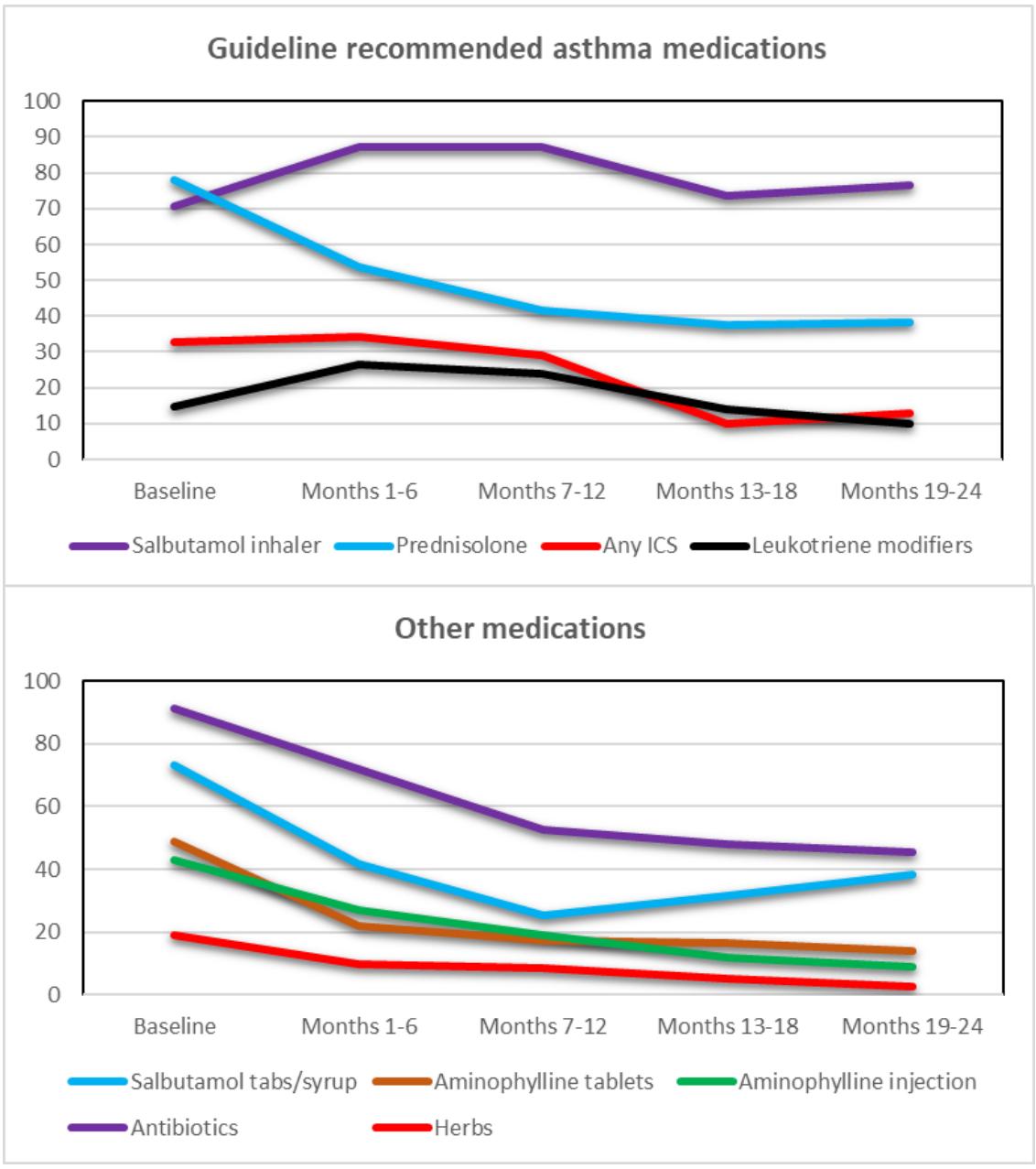
Ethics approval was obtained from the Mulago Hospital Research and Ethics committee and the Uganda National Council for Science and Technology. Participants provided written informed consent and were free to terminate study participation at any time during the study. For children aged 5-7 years parental/guardian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

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.

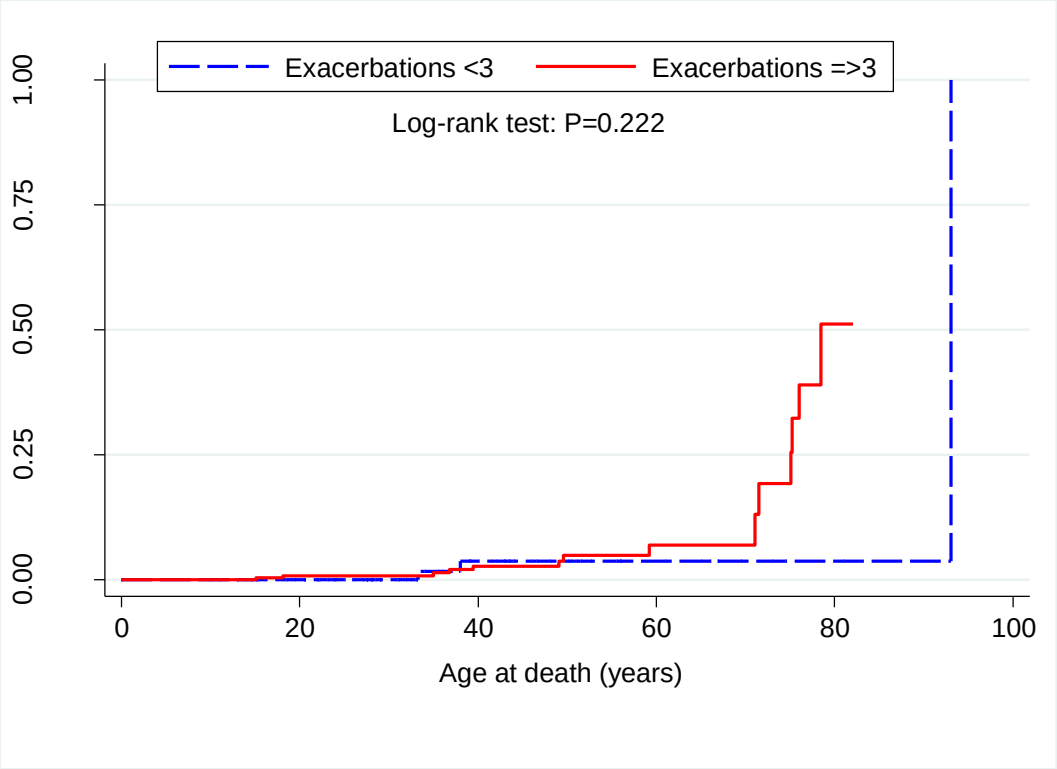


ICS=inhaled corticosteroids

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 rateΦ (deaths per 1000 years) 95% CI**	**Incidence rate ratio95% 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

Φ 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**	**Probable 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
5.	She developed an attack and passed on at home.	Asthma	<3
6.	Developed respiratory problems and died	Asthma	<3
7.	Developed cough and fast breathing, had a high blood pressure, got a stroke, then passed on	stroke	≥3
8.	Suddenly developed an attack & died shortly afterwards.	Asthma	≥3
9.	Developed an attack and died shortly afterwards	Asthma	≥3
10.	Developed an asthmatic attack after 3weeks of discharge and passed away.	Asthma	≥3
11.	Developed a severe asthma attack at home and shortly passed away	Asthma	≥3
12.	Had body swelling and died	Heart failure.	<3
13.	Had progressively worsening of chest pain and difficulty in breathing and suddenly stopped breathing	Heart failure or cardiac cause	≥3
14.	Had no respiratory symptoms but developed abdominal distension and died on arrival in the hospital	Intestinal obstruction	≥3
15.	Suddenly got an attack and died afterwards	Asthma	<3
16.	Developed cough & fast breathing was rushed to a clinic where death occurred	Asthma	≥3
17.	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 34Á51. 2007.