Title page

Full title: COPD in Africa - risk factors, hospitalisation, readmission, and associated outcomes: a systematic review and meta-analysis

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What is the key question?

What are the predictors/risk factors of COPD and healthcare utilisation in Africa?

What is the bottom line?

There is a dearth of research on the African continent despite substantial COPD-related mortality.

Why read on?

Policymakers and healthcare professionals should target local bespoke interventions and develop evidence-based guidance tailored to the demands and needs of people in the African continent to improve the management of COPD in Africa.

Abstract Word Count: 236

Main Body Word Count: 4288

1   **Abstract**

2   **Background:** This review aims to synthesise available evidence on the prevalence of COPD, associated

3   risk factors, hospitalisations, and COPD readmissions in Africa.

4   **Method:** Using the Met-Analyses and Systematic Reviews of Observational Studies guideline,

5   electronic databases were searched from inception to 1st October 2021. The quality of studies was

6   assessed using the Newcastle-Ottawa Scale. Evidence from retrieved articles was synthesised, and a

7   random-effect model meta-analysis was conducted. The protocol was registered on PROSPERO

8   (CRD42020210581).

9   **Results:** Thirty-nine studies met the inclusion criteria, with 13 included in the meta-analysis. The

10 prevalence of COPD varied between the GOLD (2%–24%), ATS/ERS (1%–17%) and MRC chronic

11 bronchitis (2%–11%) criteria, respectively. Increasing age, wheezing, and asthma were consistent risk

12 factors for COPD from studies included in the narrative synthesis. Our meta-analysis indicated that

13 prior tuberculosis (OR 5.98, 95% CI: 4.18–8.56)), smoking (OR 2.80, 95% CI: 2.19–3.59) and use of

14 biomass fuel (OR 1.52, 95% CI: 1.39–1.67)) were significant risk factors for COPD. Long-term oxygen

15 therapy (HR 4.97, 95% CI: 1.04-23.74)) and frequent hospitalisation ($\geq$3 per year) (HR 11.48, 95% CI:

16 1.31-100.79)) were risk factors associated with 30-day COPD readmission.

17 **Conclusion:** This study highlights specific risk factors for COPD risk in Africa, but also demonstrates

18 the paucity and absence of research in several countries in a continent with substantial COPD-related

19 mortality. Our findings contribute towards the development of evidence-based clinical guidelines for

20 COPD in Africa.

21 **List of Abbreviation:** ATS/ERS, American Thoracic Society/European Respiratory Society criteria;

22 BMI, body mass index; COPD, Chronic obstructive pulmonary disease; ECOPD, exacerbation of

23 COPD; FEV_1, Forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global

24 Initiative for Chronic Obstructive Lung Disease; HIV, human immunodeficiency virus; MRC,

25 Medical Research Council breathlessness scale; TB, tuberculosis

26   **What is already known on this topic:** COPD and COPD-related hospital admissions are prevalent in

27   sub-Saharan Africa; yet the research on the risk factors for COPD and COPD hospital

28   admission/readmission on the continent is sparse and diverse. There is a growing knowledge of the

29   prevalence of, risk factors and predictors of COPD, COPD admission and readmission. Most of the

30   published studies are from developed countries, hence, a systematic review is needed to identify

31   predictors/risk factors of COPD, COPD admission and readmission in Africa.

32   **What does this study add:** This study provides a comprehensive and up-to-date summary of the

33   prevalence and risk factors of COPD in Africa. It also highlights the predictors of COPD admission

34   and readmission that are unique to the continent.

35   **How this study might affect research, practice or policy:** This study identified intervention

36   opportunities that policymakers and healthcare professionals could target to reduce the burden of

37   COPD in Africa.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by airflow limitation in the lungs and is associated with an abnormal inflammatory reaction of the lung to tobacco smoke, noxious particles or gases(1). COPD was ranked the fourth (out of 369) condition with the highest disability-adjusted life years in the Global Burden of Disease report in 2019(2). The Global Burden of Disease 2019 study estimated 212.3 million prevalent cases of COPD reported worldwide(3) with 3.3 million deaths(4). Furthermore, COPD is one of the top three leading causes of death worldwide(1), with 90% of COPD deaths occurring in low- and middle-income countries (4), mainly in South Asia and sub-Saharan Africa(5).

Despite growing knowledge of the incidence and prevalence of COPD globally, there are scarce data from many countries in Africa(5,6). In spite of the increasing burden of COPD in Africa being recognised as the second highest in the WHO regions category(6), there are no published reviews that systematically highlight the predictors and risk factors for COPD in Africa(7). It is therefore vital to understand these factors as COPD in Africa has been described as an "incoming storm"(8) and "the silent epidemic"(9).

There are several factors prevalent in Africa associated with COPD. Tobacco smoking is a major risk factor for the development and progression of COPD(10) with its use in Africa on the increase(11). There are 1.1 billion smokers in the world, of which 80% live in low- and middle-income countries(12). There is also an increase in the "non-smoking" COPD population in Africa, which highlights the multifactorial pathogenesis of COPD(13). Other factors associated with COPD, especially in Africa, are environmental air pollution, exposure to combustion products of biomass fuel, occupational dusts/vapours/fumes, previous pulmonary tuberculosis (TB), human immunodeficiency virus (HIV) infection, poor diet, malnutrition (including effects in utero), low socioeconomic status and childhood respiratory infections(14,15). Environmental pollution is a significant problem, with over 90% of households and individuals in rural Africa exposed to biomass fuel(16,17).

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63   COPD is one of the leading causes of emergency hospitalisation and readmission in the world(18,19).

64   Exacerbation of COPD has been reported to be one of the main reasons for admission and readmission

65   of patients to hospital in high-income countries, with severe negative impacts on the patient and the

66   healthcare system(20). Prevention of exacerbation of COPD has been recognised as an international

67   priority in improving the prognosis of COPD and reducing associated healthcare costs(19,21). Two

68   recent systematic reviews on readmission for COPD focused on studies in developed countries with

69   none from African countries to date(20,22), highlighting the need to gather and synthesise evidence

70   from a continent with a high COPD burden to complement existing knowledge.

71   Although there has been a consensus on the importance of identifying risk factors for COPD and

72   healthcare utilisation in Africa(15,23), there is no comprehensive review summarising these risk factors

73   implicated in the development of, and hospitalisation for COPD in Africa. The available systematic

74   reviews have focused on the prevalence, diagnosis, and burden of COPD(6,24-27). The present

75   systematic review aims to summarise identified predictors/risk factors of COPD and healthcare

76   utilisation in Africa and review clinical characteristics and outcomes.

77   **Methods**

78   This study was reported following the Meta-Analyses and Systematic Reviews of Observational Studies

79   (MOOSE) Guidelines(28) The protocol was registered on PROSPERO (Reg. No.: CRD42020210581).

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81   **Data sources and search strategy**

82   We searched four electronic databases (Medline, Scopus, Embase and Cumulative Index to the Nursing

83   and Allied Literature (CINAHL) for relevant papers from the inception date to 1st October 2021. We

84   used four main search keywords ("COPD", "risk factors/consequences", "admission/readmission" and

85   "Africa") as 'concepts' based on previous systematic reviews relevant to the topic(20). Alternative

86   terms and synonyms for each of the key concepts were identified as free-text terms and used to search

87   in the databases as title and abstract. Database-specific controlled vocabulary/subject headings were

88   also used in the search (Table S1). Detailed information on the search strategy can be found in the

89   Supplement table (Table S2). Relevant studies identified through the reference list of eligible papers

90   were also included.

Eligibility criteria

92   Studies were included based on the following inclusion criteria:

93   • included the numerical estimates of the prevalence of risk factors/predictors/causes for COPD

94   or COPD admission or readmission; admission/readmission (s) of COPD clearly defined as one

95   or more admission where COPD was the primary diagnosis for the admission/readmission (s);

96   and

97   • undertaken in any of the 54 African countries.

98   Studies were excluded based on these criteria:

99   • were conference abstracts, editorial reports and letters, theses or, reviews;

100   • described the implementation of interventions or programs beyond normal care;

101   • were published in any language other than English; or

102   • undertaken in countries that are not in Africa.

Study definitions

104   COPD has been previously described based on both clinical and pathological presentations such as

105   chronic bronchitis and emphysema(29). These definitions do not explain the physiological impairment

106   of the lungs that is manifest by reduced expiratory volume linked to the vital capacity of the lungs. A

107   clear definition of COPD based on spirometry measures (a post-bronchodilator ratio of forced

108   expiratory volume in one second (FEV_1) to forced vital capacity (FVC) of less than 70% (FEV_1/FVC

109   <0.7)) has been provided by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (1)

110   and the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines(30) (Table

111   S3). It has been acknowledged that the presence of mucus hyper-secretion seen in chronic bronchitis

112   can occur without airflow limitation in some patients. Hence chronic bronchitis, or the occurrence of

113   cough and sputum production for at least three months in two consecutive years in a person in whom

114   other causes of chronic productive cough have been excluded has been used in studies(1). For the

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purpose of this review, COPD definition will be based on spirometry (1 and 2) and chronic bronchitis measurement will be termed the non-spirometry (3) measure:

1. The GOLD criteria (1);
2. The American Thoracic Society/European Respiratory Society (ATS/ERS) criteria (30), (GOLD and ATS/ERS criteria both defined as a post-bronchodilator ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) of less than 70% (FEV_1/FVC <0.7));
3. The British Medical Research Council (MRC) definition of chronic bronchitis, defined as "chronic productive cough on most days for three months in two consecutive years in a person in whom other causes of chronic productive cough have been excluded" (1)

Study selection and data extraction

Studies were exported into the Rayyan QCRI web app for systematic reviews following the removal of duplicates in EndNote X9 (Thomson Reuters, USA). Two authors (CN and KO) independently screened titles and abstracts of potential studies. The full text of eligible articles following the initial screening were independently reviewed by two authors (CN and KO) to ensure included studies met the eligibility criteria. Disagreements on selected papers between independent reviewers were resolved by a third author (SB). Data were reviewed and extracted from eligible studies according to a standardised format based on variables of interest, such as study population, study design, age, gender, smoking status, the prevalence of COPD and readmission rates. The adjusted odd ratio (OR) measurements of association were extracted from the included studies.

Risk-of-Bias assessment

Two authors (CN and KO) independently assessed the methodological quality of each included study using the Newcastle-Ottawa Scale(31) for cohort studies and adapted form for cross-sectional studies(32,33). These tools are mainly employed for the appraisal of non-randomised studies. The scale evaluates the selection, comparability and outcome of the studies, using a 'star' system with a maximum

140   of nine stars for each study(31). Two authors (CN and KO) independently assessed the quality of the

141   studies and discrepancies were resolved by consensus (CN, KO and SB)

142   *Data synthesis*

143   The heterogeneity and inconsistencies in reporting risk factors across studies prevented the inclusion of

144   all the results from the studies retrieved in the subsequent meta-analysis. The meta-analysis was

145   conducted using summary data from 13 studies to synthesise adjusted odds ratios for risk factors where

146   results were reported consistently. The pooled adjusted odd ratios and 95% confidence intervals were

147   estimated in a meta-analysis if at least five studies reported results that were sufficiently similar(34).

148   Only studies that used the same reference category for the smoking variable were included in the meta-

149   analysis. Similar analyses were performed for risk factors of COPD admission/readmission. The

150   heterogeneity of included studies was addressed by applying the random-effects model in Stata 16.0,

151   using the I^2 statistic to examine between-study heterogeneity. The heterogeneity was substantial if the

152   value of I^2 was >50% and having a p value of >0.1 was considered an indicator of lack of heterogeneity.

153   **Results**

154   The search identified 552 papers, of which 87 were duplicates and excluded. Following the initial

155   screening of 465 titles and abstracts, 149 full-text articles were assessed for eligibility and 39 papers

156   met the inclusion criteria. The detailed selection process is shown in Figure 1. The result of the quality

157   assessment showed thirty-eight studies (97.4%) had five or more stars with one study (2.6%) having

158   three stars (Table S4).

159   *Study characteristics*

160   Table 1 shows the summary of relevant characteristics from 39 studies, which included 100,722

161   participants. Thirty-four of the studies (87%) were cross-sectional studies, with two studies (5%)

162   conducted prospectively and another three (8%) conducted retrospectively. The studies were conducted

163   across 14 of the 54 countries (26%) in the African continent. Five (out of 18) East African countries

164   contributed the largest number of studies (n=16) (15,17,35-48), followed by four (out of 6) North

165   African countries with eight studies(49-56), two (out of 16) West African countries contributing seven

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166   studies(57-62) and one (out of 5) Southern African countries(63-66) and two (out of 9) Middle African

167   countries(67-70) both contributing four studies each. Seven studies were conducted in

168   Uganda(15,37,42-46); six in Nigeria(57-60,62,71); four in South Africa(63-66); three each in

169   Cameroon(68-70), Egypt(49,55,56), Morocco(52,53,55), Tanzania(17,41,48) and Tunisia(50,51,55);

170   two each in Algeria(54,55), Ethiopia(35,47), Malawi(36,38), Rwanda(39,40) and one each in Cape

171   Verde(61) and Democratic Republic of Congo(67). Thirty-five of the included studies (92%) were

172   published within the last decade (2010–2020).

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174 **Table 1. Characteristics of included studies**

First Author Year	Region	Study design	Population studied	Number of patients	Mean age (years)	Gender (Male %)	Current smoker (%)	Former smokers (%)	Biomass exposure (%)	COPD prevalence rate (%) Spirometric GOLD criteria	Spirometric ATS/ERS criteria	Non Spirometric MRC Chronic Bronchitis criteria	Rate of COPD admission/ readmission
Adeniyi, 2017(57)	Nigeria§	R		502		54.0							7.5 with 1 admission within 5 years
Akanbi, 2015(58)	Nigeria§	CS	Hospital based	356	44.5	41.0	3.7	17.1		15.4	12.1		
Anbesse, 2020(35)	Ethiopia*	P		71	60.0	69.0	35.2	19.7					6.0 readmission with 30 days
Badway, 2015(49)	Egypt‡	CS	Mixed	2,400		70.0	50.4	6.9	10.8	6.7			
Buist, 2007(63)	South Africa¥	CS	Mixed	847	53.6	37.0	48.8	21.3		23.8			
Daldoul, 2013(50)	Tunisia‡	CS	Mixed	807	59.5	46.7	28.6	13.3		7.8	5.3		
Denguezli, 2016(51)	Tunisia‡	CS	Mixed	807		46.2	27.3			7.8			
Desalu, 2011(59)	Nigeria§	CS	Rural	391	55.5	34.5	2.6	9.2				5.6	
Desalu, 2010(60)	Nigeria§	CS	Rural	269	55.5				59.9	7.4			
Ehrlich, 2004(64)	South Africa¥	CS	Mixed	13,826				3.6				2.6	
El Rhazi, 2016(52)	Morocco‡	CS	Mixed	966	56.1	43.0	8.0	17.0	38.6	12.6	8.9		
Fullerton, 2011(36)	Malawi*	CS	Mixed	374	46.0	39.7	13.9	7.5			13.6		
Gathuru, 2002(71)	Nigeria§	CS	Urban	270	47.6	57.6	10.8				9.3		
Iyaloo, 2020(65)	South Africa¥	CS	Occupational	149						12.8			
Kayongo, 2020(37)	Uganda*	CS		722	48.0	40.3	5.4		88.5		6.22		
Laraqui, 2018(53)	Morocco‡	CS	Occupational	924	40.8	100.0	46.6	23.3		4.1			
Magitta, 2018(17)	Tanzania*	CS	Rural	496	51.8	53.0	5.4	19.8	99.5	17.5			
Martins, 2009(61)	Cape Verde§	CS	Urban	274	41.5	35.0	5.8	6.6	45.3	8.4			
Mbelambela, 2020(67)	DR Congo∞	CS		235		0.0					12.3		

Meghji, 2016(38)	Malawi∗	CS	Urban	749	41.9	42.1				4.2			
Musafiri, 2018(39)	Rwanda∗	P		436	32.2				68.3			10.7	
Musafiri, 2011(40)	Rwanda∗	CS	Mixed	1,824	38.3	48.1	16.7	15.8	60.3		4.5		
Mwaiselage, 2005(41)	Tanzania∗	CS	Occupational	222	40.0					12.2			
Ngahane, 2015(68)	Cameroon∞	CS		300		0				1.6			
North, 2019(42)	Uganda∗	CS		565	39.0	38.0	10.0	19.0		2.0			
Nuwagira, 2020(43)	Uganda∗	CS		95	39.0	60.0	1.0	24.0		23.0			
Obaseki, 2016(62)	Nigeria§	CS	Rural	1,148		37	2.3	8.4			7.7		
Pefura-Yone, 2016(70)	Cameroon∞	CS	Urban	1,287	34.4	48.1	9.4	6.8	47.6		2.4		
Pefura-Yone, 2015(69)	Cameroon∞	CS	Urban	922	42.6	32.3	7.0	8.1		5.1	1.4		
Pienaar, 2015(66)	South Africa¥	R		178	63.0	57.9	34.0	65.7					56.2 with 1 admission, 24.7 with 2 admissions, 19.1 with ≥3 admissions,43.8 with ≥2 readmissions within 12 months
Ramdani, 2020(54)	Algeria‡	R		120	74.3	96.0							46.3 with 1 readmission, 19.5 with 2 readmissions, 34.1 3-12 readmissions within 10 years
Said, 2015(56)	Egypt‡	CS		363		78.0	73.8	5.5		9.6	17.4		
Siddharthan, 2018(45)	Uganda: ∗ Kampala	CS		596	44.2	48.7	8.7		93.5		1.7		
	Masindi	CS		414	49.7	50.0	36.2		92.8		15.5		
	Nakaseke	CS		721	49.1	45.9	6.9		99.6		7.4		
Siddharthan, 2019(44)	Uganda∗: Kampala	CS		665	44.1	47.8			93.6		1.5	2.2	
	Nakaseke	CS		837	49.1	45.4			99.6		6.1	3.5	
Tageldin, 2012(55)	Algeria‡, Egypt‡ Morocco‡ Tunisia‡	CS		62,086		51.0						3.7 3.5 2.2 3.7	
van Germert, 2015(46)	Uganda∗	CS	Rural	588	45.2	49.0	20.7	14.8	93.0	12.4	16.2		
van Germert, 2016(15)	Uganda∗	CS	Rural	588	45.2	49.5	20.7	14.8	93.0		16.2		
Woldeamanuel, 2019(47)	Ethiopia∗	CS		734	39.2	57.4	9.0	2.7	82.0	17.8			
Zoller, 2018(48)	Tanzania∗	CS	Mixed	598	46	52.0	15.0	13.0	85.0	5.0	4.0		

175   ATS/ERS American Thoracic Society/European Respiratory Society; MRC British Medical Research Council; CS Cross-sectional study; GOLD Global Initiative for Chronic
176   Obstructive Lung Disease; P Prospective study; R Retrospective study; § West Africa; ‡ North Africa; ∗ East Africa; ¥ South Africa; ∞ Middle Africa

Prevalence of COPD, COPD admission and readmission

Fourteen studies described COPD prevalence based on GOLD spirometric criteria(17,37,38,40-42,47,49,51,53,60,63,65,68), ten on ATS/ERS spirometric criteria(15,36,37,40,43,45,52,62,67,70) while seven studies were on both GOLD and ATS/ERS criteria(46,48,50,52,56,58,70). Five studies utilised the MRC description of chronic bronchitis(39,44,55,59,64) with one reporting both chronic bronchitis (MRC) and COPD (ATS/ERS) criteria(44). Thirty-one studies reported a total of 41 rates of COPD prevalence based on spirometry while five studies reported nine rates of chronic bronchitis prevalence based on MRC criteria (Table 1). The prevalence of COPD ranged from 2% to 24% (GOLD criteria) and 1% to 17% (ATS/ERS criteria). The prevalence of chronic bronchitis ranged from 2% to 11% (MRC criteria).

Eight studies from North African countries (4 out of 8) reported on the prevalence of COPD based on GOLD spirometry criteria ranging from 4.1% to 12.6%, ATS/ERS criteria from 5.3% to 17.4%, and non-spirometry chronic bronchitis criteria from 2.2% to 3.7%. Twenty-eight studies from the sub-Saharan African countries reported the prevalence of COPD via GOLD criteria from 1.6% to 23.8%, ATS/ERS criteria from 1.4% to 17.4% and chronic bronchitis MRC criteria from 2.2% to 10.7%.

Two studies reported the rate of COPD admission as 56% over 12 months(66) and 8% over 5 years(57) study periods respectively. Three studies reported the rate of COPD readmission as 6%(35) within 30 days post-discharge, 44% over 12 months(66) and 46% over 10 years of study period(54).

Risk factors for COPD, COPD admission and readmission

Twenty-one studies reported 12 possible risk factors for COPD(15,17,37-41,43,45-47,50,51,56,58,59,62,64,67,69,70). Of these, three factors (biomass fuel, TB, and smoking) were considered for pooled adjusted ORs as the remaining factors were examined in fewer than five studies(34). No study reported on risk factors for COPD admission.

Long-term oxygen therapy (HR 4.97, 95% CI 1.04-23.74) and frequent hospitalisation (≥3 in a year) (HR 11.48, 95% CI 1.31-100.79) were found to be risk factors associated with 30 days COPD

202 readmission(35). Detailed summaries of the risk factors associated with COPD and COPD readmission

203 are presented in Tables S5 and S6.

204 *Meta-analysis*

205 Meta-analysis was not performed on all results because of the lack of data on admissions/readmissions

206 and the heterogeneity of selected studies. We included 13 studies comprising 23,035 patients in the

207 meta-analysis for the examination of COPD risk factors. Seven of the studies with 18,314 patients

208 reported smoking as a risk factor, seven studies comprising 18,600 patients reported the use of biomass

209 as fuel as a risk factor while five studies with 17,114 patients reported history of TB as a risk factor.

210 The pooled adjusted OR indicates that previous pulmonary TB (OR 5.98, 95% CI 4.18–8.56), smoking

211 (OR 2.80, 95% CI 2.19–3.59), and use of biomass as fuel (OR 1.52, 95% CI 1.39–1.67) are significant

212 risk factors for COPD in Africa. These are presented using forest plots (Figures 2a-2c). The

213 heterogeneity between studies was not significant with I^2 values of 0% (95% CI: 0%, 61%, p=0.84),

214 15% (95% CI: 0%, 61%, p=0.31) and 37% (95% CI: 0%, 70%, p=0.12) for TB, smoking status, and

215 biomass as fuel respectively (Figures 2a–2c).

216 *Narrative synthesis for risk factors for COPD*

217 *Older age*

218 Thirteen out of 19 studies that examined the relationship between age and COPD, associated older age

219 across various age ranges (≥30 years to ≥74 years) with increased risk of COPD. Meghji *et al.* reported

220 that the odds of having COPD within the age range of 50–59 years compared to ≥60 varied significantly

221 from OR of 4.66 to 10.12(38). This was confirmed in research by Magitta *et al.* where the risk of COPD

222 significantly increased in patients aged between 51–60 (OR 9.66, CI 95% 4.79–18.25) compared to

223 those between 41–50 (OR 4.02, 95% CI 1.10–14.66) in relation to those aged between 30-40(17).

224 Desalu *et al.* also reported a significant association between older age (65–74 and ≥74) and COPD

225 compared to those <35 years. However, ages between 55–64 had a significant protective effect with an

226 OR of 0.20 in comparison to <35(59).

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Other risk factors

229 Three studies reported patients with a wheeze to be more likely to develop COPD(46,56,70) while no

230 association was found in patients with chronic cough and sputum production(15,46,56,70). For example,

231 Pefura-Yone *et al* found patients with lifetime wheeze to have almost 3-fold increased odds of

232 developing COPD compared to those without lifetime wheeze(70). Asthma was associated with

233 increased risk for COPD in two studies(51,62) while no association was found with other comorbidities

234 (such as hypertension, heart failure, pneumonia, and diabetes) and COPD. Several studies investigated

235 sex (n=13), ethnicity (n=2), BMI (n=8), HIV (n=6), living in urban areas (n=3), educational level (n=14)

236 and occupational exposure to dusts, gases or fumes (n=6) as risk factor for COPD but the results were

237 inconsistent. One study found men to have a 3.0 odds of COPD compared to being female(40) however,

238 another ten studies found no association between sex and COPD.

239 **Discussion**

240 This is the first systematic review to examine and summarise the risk factors for COPD and COPD

241 admission in Africa. Our meta-analysis showed that history of TB, smoking and use of biomass fuel are

242 associated with an increased risk of COPD. Increasing age, wheezing and comorbid asthma are also

243 risk factors for COPD. We found that the prevalence of COPD ranged from 1% to 24% depending on

244 the assessment criteria and setting. We estimated, for the first time the prevalence of COPD in

245 Africa and we also identified COPD risk factors that are of importance on the continent.

246 Nevertheless, these estimates were from only 14 out of the 54 countries. This highlights the

247 urgency and need for more research work to be conducted in COPD across Africa, considering that 90%

248 of the COPD-related mortality rate occurs in Africa.

249 Our study reports the prevalence of COPD ranging from 1% to 24% is consistent with previous reviews

250 that reported COPD prevalence in sub-Saharan African countries between 4% and 25%(24,25). Another

251 review reported COPD prevalence in Africa in all spirometry-confirmed cases to be 13.4% and non-

252 spirometry-confirmed cases to be 4.0%(24). This was different to our result on spirometric confirmed

253 cases and non-spirometric confirmed cases. The wide variation in the prevalence of COPD in Africa

254   may be due to variations in the study population and setting, age of participants and criteria utilised for

255   diagnosis(14). This is similar to the result of a recent systematic review that focused on developed

256   countries(20).

257   The 12-month and five years admission rates for COPD were 56% and 8%, respectively, which are

258   inconsistent with other studies in the literature. The rate of readmission ranged from 6%–46%,

259   depending on the follow-up period. Other reviews have only considered readmission from COPD in

260   developed countries(20,22). The COPD readmission rate reported in African populations is lower for

261   30 days readmission (6.0%) compared to developed countries that varied from 8.8% to 26.0%(22),

262   however, there was consistency in 1-year readmission. It is vital to highlight the lack of studies on

263   readmissions in Africa, and the challenges accessing affordable hospital care for those in need. Three

264   studies reported COPD readmission (1= 30-day, 1= 1-year and 1= 10-years). On the contrary, 32 studies

265   in developed countries reported 30 days, 90 days and 1-year all-cause COPD readmission(22) and 54

266   studies reported 30 days, 90 days and 1-year COPD-related readmission(20).

267   Reasons for the differences in the figures observed between Africa and developed countries may include

268   the economic burden of COPD due to poor access and affordability to hospital healthcare for many

269   populations from low socioeconomic areas. Another plausible reason could reflect the widespread

270   under-recognition and under-diagnosis of COPD(1). There is also diversity both within and between

271   African countries (e.g. Northern African countries vs sub-Saharan African countries). Our study clearly

272   highlights the importance of further research in this area with only 14 countries (out of 54) contributing

273   to the studies.

274   Consistent with the literature, our results found previous TB infection to be independently associated

275   with COPD(72). TB can result in airflow obstruction meeting the spirometric criteria for COPD. TB is

276   known to trigger airway inflammatory response that consequently results in a decrease in lung

277   volume(72). There is the inflammatory response of TB known by its increased oxidative stress in the

278   airways and lung parenchyma which are vital pathological processes in the development and

279   progression of COPD(72). The high prevalence of TB worldwide especially in many developing

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280   countries denotes a considerable public health significance both to epidemiologists and healthcare

281   providers.

282   Asthma was found to be strongly associated with the development of COPD. Poorly controlled asthma,

283   for example in the absence of access to affordable therapy, can result in airflow obstruction that meets

284   the spirometric criteria for COPD. This is in line with a report from the Tucson study that found patients

285   with asthma to have a 12-fold higher risk of developing COPD compared to those without asthma(73).

286   Although the reversibility of pulmonary obstruction in response to treatment is a hallmark of asthma, it

287   has been shown to decrease over time in some asthmatic patients, to the point of irreversible or only

288   partially reversible airway obstruction(74). Systematic reviews have found an increased frequency of

289   COPD exacerbation and hospitalisation in patients with asthma(75,76). This increases the disease

290   burden for patients with COPD. Clinical respiratory guidelines that are tailored to the needs and

291   demands of African countries by the global community may improve the diagnosis and management of

292   COPD but are often lacking(77). Accessibility, availability and affordability of COPD and respiratory

293   medicines will go a long way in the management of COPD.

294   The use of biomass fuel for cooking and heating was found to be a significant risk factor for COPD.

295   Globally almost three million people utilise biomass and coal as their essential source of energy for

296   cooking, heating, and other household requirements(78). Over 90% of households in rural Africa are

297   exposed to biomass fuel with women and young children, particularly at increased risk of exposure

298   during food preparation(17). Exposure to solid fuels for cooking is associated with premature 3.8

299   million deaths a year(79). Twenty-five percent of deaths from COPD in adults in low- and middle-

300   income countries are due to exposure to household air pollution(79). Cooking in poor ventilated

301   kitchens was associated with a four-fold increase in development of COPD(47). In poorly ventilated

302   dwellings, indoor smoke can be 100 times higher than appropriate levels for fine particles(79). There is

303   also the impact of pollution from industrialisation comprising of fossil fuel-driven machineries with

304   limited implementation of safety and health standards in many settings. This highlights the potential for

305   effective policies and strategies to reduce the exposure and impact of biomass fuels and the COPD

306   burden of disease.

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307   Seven studies found strong associations between smoking and COPD. Smoking is recognised to be the

308   most important cause of COPD in high-income settings. This relationship was substantial in subgroups

309   of current smokers, former smokers and combining current and former smokers. Forey *et al* in a meta-

310   analysis comprising of 218 studies demonstrated a clear relationship between smoking (for ever, current

311   and former smoking) and COPD(80). Many of the African countries have lower tobacco taxation rates,

312   weaker smoke-free policies with less stringent tobacco advertising restrictions in comparison to higher

313   income and developed countries. Hence, they are less likely to implement programs aimed at prohibiting

314   smoking in public places(11). Urgent action is required by all stakeholders including governments in

315   implementing and advocating prohibition of smoking in public places.

316   The results of individual studies have demonstrated that the odds of having COPD are greater in older

317   age groups compared to younger age groups. This finding is unsurprising and consistent with previous

318   reports(20,22). The average life expectancy in African countries has increased since 2000 from 50.8

319   years to 61.2 years in 2016(81). This increase suggests that the burden of COPD will also be increasing

320   and therefore requires urgent attention. The higher COPD risk among individuals in the older age

321   category may be an indication of cumulative exposures during lifetime or aging of the airways and

322   parenchyma associated with structural changes in COPD(1). Interestingly, the age range included in

323   some studies were as low as 30 years suggesting early onset, with early and continuous exposure to

324   biomass and noxious fumes. These in combination with poor lung growth, and development associated

325   with poverty and inadequately treated respiratory infections increased the burden of COPD disease.

326   African governments need to implement urgent policies to reduce airborne exposures, tobacco smoke

327   and indoor and outdoor pollution.

328   Two papers reported risk factors for readmission of COPD (35,66) with one reporting only p values for

329   the multivariate analysis. Anbesse *et al.* found long-term use of oxygen therapy (a marker of respiratory

330   failure, but a treatment not widely available in Africa) and frequent hospitalisation (≥3) in a year to be

331   associated with an increased risk of COPD readmission(35). This is consistent with a recent systematic

332   review undertaken in developed countries(20). Patients on long-term oxygen therapy are likely to have

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333 severe and advanced disease thereby increasing their risk of readmission. Similarly, frequent

334 hospitalisation may indicate sub-optimal management or disease severity.

335 There are limitations to this study. We limited our literature search to studies published in English;

336 hence, it is possible that we might have missed studies published in other languages. In addition, Africa

337 is geographically large and diverse with varying health determinants and socioeconomic factors. That

338 diversity extends to differences within countries such that context varies greatly. The covariates

339 reported in the studies included in the metanalysis were not uniform, and the OR derived from various

340 studies was adjusted for different covariates. There is also the variation in the method of diagnosing

341 COPD which reflects the diversity of formal and informal healthcare system found in most African

342 countries. The diverse healthcare system is intertwined with social, cultural, and economic/affordability

343 issues which are strong barriers to early assessing of appropriate healthcare services. Appropriate

344 management of COPD will require appropriate diagnosis involving access to spirometry. A majority of

345 healthcare facilities in Africa lack spirometry and must rely solely on clinical features for diagnosis,

346 perhaps supported by case-finding tools(82). There is also the issue of affordability of the life-long

347 treatments for appropriate management of COPD. Adherence will continue to be severely affected by

348 affordability of health cost imposed on poor income households. The availability of COPD therapy at

349 an affordable price will be a starting point in the prevention and management of COPD, as will the

350 effective implementation of guidelines(83). Further studies in partnership with international

351 communities are urgently needed to tackle this global public health issue. We recognise that the causes

352 of poorly reversible airflow obstruction in LMIC settings are diverse and that not everyone meeting

353 spirometric criteria for COPD has an exposure-driven airway disease. In addition, respiratory exposures

354 in LMIC may cause manifestations such as emphysema that are not necessarily associated with poorly

355 reversible airflow obstruction despite being part of the COPD definition. These limitations are rarely

356 adequately addressed in the individual studies we have summarised and are important areas for future

357 research.

358 **Conclusion:**

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359   The prevalence of COPD is higher based on GOLD criteria (2%–24%) compared with ATS/ERS criteria

360   (1%–17%), and MRC chronic bronchitis criteria (2%–11%). Comorbidity (TB and asthma), smoking

361   and use of biomass as fuel are significant risk factors for COPD in Africa. Long-term use of oxygen

362   therapy and frequent hospitalisation ($\geq$3) in a year are associated with increased an risk of COPD

363   readmission. Further studies are needed for clearer reporting of the magnitude of the problem. These

364   identified factors potentially guide the development of evidence-based guidance and culturally

365   acceptable local interventions tailored to the demands and needs of various regions on the African

366   continent.

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