ORIGINAL RESEARCH

Factors Associated with Chronic Obstructive Pulmonary Disease: A Hospital-Based Case–Control Study

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Purpose: Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. In this paper, we determined risk factors for COPD among patients presenting to pulmonology and medical outpatients' clinics of Mbarara Regional Referral Hospital (MRRH).

Methods: In this case–control study, cases were patients with COPD confirmed by spirometry and controls were those with normal spirometry. The two groups were matched by age and gender.

Results: We enrolled 123 participants, of whom 41 were cases and 82 controls. A total of 51 women (41.5%) and 72 men (58.5%), of whom 25 were male cases (61%) and 47 were male controls (57%), were included. The results of our study suggest that the variables associated with the presence of COPD among participants attending MRRH were a history of having ever smoked and a prior history of atopy. This brings to our attention the fact that smoking remains a major risk factor for COPD in this setting, just as it is in developed countries.

Conclusion: Our study has shown that the factors associated with COPD are smoking and a history of atopy. Patients with a history of asthma and tuberculosis are also probably more likely to develop COPD than those without similar disease conditions.

Keywords: chronic bronchitis, emphysema, asthma, smoking

Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a chronic respiratory disorder marked by persistent respiratory symptoms and airflow limitations. COPD significantly affects general well-being, which is important in view of its increasing incidence and associated morbidity and mortality. In COPD, the normal airflow is irritated by episodes of respiratory symptoms, with deteriorating intensifications that add to disease progression.[1]

Airflow obstruction and persistent respiratory symptoms are the hallmarks of COPD. Tobacco smoking is the main cause of COPD, but not the only one.[2] A post-bronchodilator forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio under 0.70 is expected for a diagnosis of COPD.[3] A multifaceted management strategy that includes counseling and pharmacotherapy for smoking cessation, pulmonary rehabilitation, the treatment of comorbidities, the administration of influenza and pneumococcal immunizations, and the prescription of long-term oxygen therapy in hypoxemic patients should be complemented by inhaler therapy.[4]

COPD is one of the leading causes of death worldwide.[5] As well as being one of the most significant causes of morbidity worldwide, COPD also has a significant impact on the patient's health and socioeconomic situation.[6] During 2005 to 2013, disability-adjusted life-years (DALYs) due to COPD ranked from eight to fifth among all causes.[7]

The burden of COPD in sub-Saharan Africa has been poorly studied. The main reasons why COPD prevalence studies are rare are the general lack of standardized epidemiological instruments and the need to perform good-quality post-bronchodilator spirometry, which requires considerable expertise and experience.[8] In low- and middle-income countries (LMICs), COPD is recognized as a major health issue. There were 3.8 million deaths due to COPD in 2019, with around 90% of these occurring in LMICs. The WHO assesses that around 251 million individuals have COPD overall and that this burden is increasing[9]. Smoking is the main risk factor for COPD.[10] The burden in LMICs is thought to be higher than in developed countries owing to relatively low COPD awareness. Although the use of biomass fuel has been suggested as a significant risk factor,[11] any proof to support this declaration is currently weak. Other risk factors include exposure to dust and a history of serious lung infections, such as tuberculosis (TB).[12] A study in Uganda reported that COPD was more prevalent in young people and women who were non-smokers.[13] This further suggests that this population may be exposed to non-traditional COPD risk factors which have not been studied in depth.

This case–control study, therefore, aimed to determine risk factors for COPD among patients attending pulmonology and medical outpatients' clinics of Mbarara Regional Referral Hospital (MRRH).

Materials and Methods

In this case–control study, cases were patients with COPD confirmed by spirometry using the NHANES III prediction equation[14] and controls were those with normal spirometry. The two groups were matched by age and gender.

The study included adults aged 18 years and above presenting to pulmonology and medical outpatients' clinics of MRRH in south-western Uganda. The participants in the control group were individuals who presented to medical outpatients' clinics of MRRH, who had no history of respiratory symptoms. Individuals in the control group were aged 18 years or more, with normal spirometry, matched with cases by age (±5 years) and gender. We enrolled two controls for every case. Cases also completed 6 minute walk tests.

Our case–control study aimed to determine whether COPD is associated with past exposure to risk factors such as cigarette smoking. Cases were patients with COPD and controls were those without COPD or any respiratory symptoms enrolled from medical outpatient clinics. In a single study by Manoj Kumar Meghwani from India in 2013,[15] 36.3% of participants were exposed to cigarette smoking in the control group. We wished to detect an odds ratio of 3 with a power of 80%, and recruited two controls for each case.

Ethical Considerations

The research proposal was presented to and approved by the following bodies: the Department of Internal Medicine, the Faculty Research Ethics Committee of Mbarara University (FREC MUST), and the Institutional Research Ethics Committee. Informed consent was obtained from each study participant in the form of a fingerprint or signature. The right to withdraw from participation in the study without any consequences to the participant was guaranteed from the start. Study data were kept under lock and key, and only responsible clinicians were able to access patient information for clinical purposes. Patient identification numbers were used for data entry to ensure confidentiality. The investigation was low risk as no substances were administered to patients in any experimental manner. In addition, patients benefited from free spirometry work-up during this study. The study was conducted according to the principles of the Declaration of Helsinki.

Results
Description of Study Participants

We enrolled 123 participants, of whom 41 were cases and 82 controls. Participants' baseline characteristics are shown in Table 1. A total of 51 women (41.5%) and 72 men (58.5%), of whom 25 were male cases (61%) and 47 were male controls (57%), were included. These proportions were compared by the chi-squared test, giving a *p*-value of 0.698, implying that the groups (both cases and controls) were similar for the gender variable. The lower limit for age was 27 years and the upper limit was 90 years. The median age for cases was 70 years (25th percentile 56 and 75th percentile 78 years). Controls had a median age of 68 years (25th percentile 55 and 75th percentile 77 years). Twenty-five cases (61%) and 48 controls (59%) were subsistence farmers; when comparisons between different occupations were made using the

Table 1 Demographic Characteristics

Variables	Cases N=41	Controls N=82	*p*-Value
Gender, n (%)			
Male	25 (61)	47 (57)	0.698
Female	16 (39)	35 (43)	
Age (years), median (IQR)	70 (56–78)	68 (55–77)	0.654
Marital status, n (%)			
Single	4 (10)	1 (1)	0.142
Widow/widower	8 (19)	14 (17)	
Separated	2 (5)	4 (5)	
Married	27 (66)	63 (77)	
Level of education, n (%)			
Tertiary	7 (17)	9 (11)	0.653
Secondary	7 (17)	20 (24)	
Primary	15 (37)	32 (39)	
None	12 (29)	21 (26)	
Occupation, n (%)			
Subsistence farming	25 (61)	48 (59)	0.968
Farming (with animals)	4 (10)	10 (12)	
Business	2 (5)	5 (6)	
Others	10 (24)	19 (23)	
Address, n (%)			
Mbarara	12 (29)	38 (46)	0.221
Isingiro	10 (24)	12 (15)	
Bushenyi	2 (5)	6 (7)	
Others	17 (42)	26 (32)	
BMI (kg/m^2), median (IQR)	21 (19–30)	22 (19–25)	0.750
Pre FEV$_1$/FVC, median (IQR)	56 (50–63)	77 (72–81)	0.000
Pre FVC (% predicted), median (IQR)	85 (72–102)	100 (89–118)	0.010
Post FEV$_1$/FVC, median (IQR)	59 (52.2–66.5)		
% Oxygen saturation post-6MWT, median (IQR)	92 (87–96)		
BODE index, median (IQR)	3 (1–5)		
% 4-year survival, median (IQR)	67 (57–80)		

Abbreviations: IQR, interquartile range; BMI, body mass index; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; 6MWT, Six-Minute Walk Test.

chi-squared test, a *p*-value of 0.968 was determined, suggesting a similar distribution of occupations among cases and controls. The other occupations included teachers, engineers, and boda riders.

In total, 22 cases (53%) and 50 controls (61%) were from the districts of Mbarara and Isingiro. The "others" category included participants from the districts of Kiruhura, Sheema, Kabale, etc. A *p*-value of 0.221 was suggestive of similar cases and controls for the address variable.

The median body mass index (BMI) for cases was 21 kg/m^2 (25th percentile 19 and 75th percentile 30 kg/m^2). Controls had a median BMI of 22 kg/m^2 (25th percentile 19 and 75th percentile 25 kg/m^2). The median pre-bronchodilator FEV_1/FVC was 56 for cases (25th percentile 50 and 75th percentile 63). Controls had a median pre-bronchodilator FEV_1/FVC of 77 (25th percentile 72 and 75th percentile 81). A *p*-value of 0.000 was determined, suggesting a difference between groups (cases and controls) for the pre-bronchodilator FEV_1/FVC variable. The median BODE index was 3 (25th percentile 1 and 75th percentile 5). The median percentage 4-year survival for the cases as derived from the BODE index was 67% (25th percentile 57 and 75th percentile 80).

Medical and Smoking Status

A summary of physician-diagnosed medical conditions and smoking exposure among cases and controls is presented in Table 2. Only four cases (10%) reported being positive for HIV, and six controls (7%) also reported living with HIV. A *p*-value of 0.639 was suggestive of having similar groups (cases and controls) with the HIV-positive variable. Six cases (15%) and two controls (2%) reported a history of a prior diagnosis of asthma. There was a difference in reported asthma between cases and controls, with a *p*-value of 0.010. Twenty cases (49%) and 19 controls (23%) reported a history of having ever had physician-diagnosed atopy. Three cases (7%) and one control (1%) reported a positive history of TB disease.

In total, 28 cases (68%) and 34 controls (41%) reported having ever smoked tobacco products; and using the chi-squared test, there was a difference between the groups (cases and controls) regarding having ever used tobacco products. The median age at the start of smoking was 15 years for cases (25th percentile 12 and 75th percentile 18 years). Controls also had a median of 15 years, but with 25th percentile of 12 and 75th percentile of 20 years. The median duration of smoking was 35 years (25th percentile 18 and 75th percentile 45 years) for cases, while controls had a median duration of 26.5 years (25th percentile 10 and 75th percentile 38 years). There were more current smokers in cases [12 (29%)] than in controls [10 (12%)]. Comparing the two groups with a chi-squared test for the current-smoking variable, a *p*-value of 0.02 was found, suggesting a difference between the groups (cases and controls).

Table 2 Medical and Smoking History

Variables	Cases N=41	Controls N=82	*p*-Value
Physician-Diagnosed Conditions			
HIV, n (%)			
Negative	29 (71)	54 (66)	0.639
Positive	4 (10)	6 (7)	
Unknown	8 (19)	22 (27)	
Asthma, n (%)			
No	35 (85)	80 (98)	0.010
Yes	6 (15)	2 (2)	
Allergy, n (%)			
No	21 (51)	63 (77)	0.004
Yes	20 (49)	19 (23)	

(*Continued*)

Table 2 (Continued).

Variables	Cases N=41	Controls N=82	*p*-Value
TB, n (%)			
No	38 (93)	81 (99)	0.072
Yes	3 (7)	I (I)	
Tobacco Exposure			
Ever smoked, n (%)			
No	13 (32)	48 (59)	0.005
Yes	28 (68)	34 (41)	
Age at start (years), median (IQR)	15 (12–18)	15 (12–20)	0.997
Quit smoking, n (%)			
No	12 (43)	4 (12)	0.760
Yes	16 (57)	23 (85)	
Years of smoking, median (IQR)	35 (18–45)	26.5 (10–38)	0.900
Current smoking, n (%)			
No	29 (71)	72 (88)	0.020
Yes	12 (29)	10 (12)	

Abbreviations: HIV, human immunodeficiency virus; TB, pulmonary tuberculosis; IQR, interquartile range.

Biomass Exposure and Environmental Pollution

A summary of the findings from the analysis of environmental exposure variables among cases and controls is presented in Table 3. Participants reported mean outdoor environmental exposure of 10±2.7 hours for cases and 11±2.4 hours for controls. Comparing this variable between the groups (cases and controls) using the Student's *t*-test, a *p*-value of 0.009 suggested a difference in the mean between the groups. The median duration of time spent cooking was 2 hours for cases (25th percentile 0 and 75th percentile 4 hours), while controls had a median duration of 1 hour (25th percentile 0 and 75th percentile 3 hours). Both cases and controls spent a median duration of 4 hours digging. The primary sources of fuel for cooking were firewood and charcoal: 34 cases (83%) and 67 controls (82%) used firewood, while seven cases (17%) and 15 controls (18%) used charcoal as a primary cooking fuel. The mean duration of primary fuel use was 45±17 years for cases and 42±16 years for controls. There was no difference in the mean duration of primary fuel use among cases and controls (*p*=0.375). In total, 21 cases (51%) and 44 controls (54%) reported having been primarily responsible for cooking in their homes. The median age at the start of cooking was 10 years (25th percentile 8 and 75th percentile 18 years) for cases, while controls reported a median of 12 years (25th percentile 10 and 75th percentile 15 years). The mean time spent by cases inside the kitchen daily was 3.8±2.2 hours, while controls spent 3.5±1.9 hours. Indoor cooking smoke exposure per year was calculated for those participants who reported being primarily responsible for cooking in their homes. Five cases (26%) and five controls (13%) were exposed to less than 500 hours of smoke per year, whereas 14 cases (74%) and 34 controls (87%) were exposed to more than 500 hours of indoor smoke per year. In addition, 24 cases (59%) and 48 controls (59%) reported having always burnt trash in their homes and gardens. The primary source of lighting in homes was reported as kerosene lamps, candles, and electricity: 33 cases (81%) and 65 controls (79%) used kerosene lamps. There was no difference between the groups (cases and controls) with regard to the primary source of light in the home (*p*=0.899).

Table 3 Biomass Exposure and Environmental Pollution

Variables	Cases N=41	Controls N=82	p-Value
Outdoors (hours per day), mean (SD)	10 (2.7)	11 (2.4)	0.009
Indoors (hours per day), mean (SD)	14 (2.8)	13 (2.4)	0.009
Hours spent cooking, median (IQR)	2 (0–4)	1 (0–3)	0.196
Hours spent digging, median (IQR)	4 (0–6)	4 (2–6)	0.196
Primary fuel, n (%)			
Charcoal	7 (17)	15 (18)	0.868
Firewood	34 (83)	67 (82)	
Duration of primary fuel use (years), mean (SD)	45 (17)	42 (16)	0.375
Cooking primary responsibility, n (%)			
No	20 (49)	38 (46)	0.798
Yes	21 (51)	44 (54)	
Age at start of cooking (years), median (IQR)	10 (8–18)	12 (10–15)	0.902
Hours per day inside kitchen, mean (SD)	3.8 (2.2)	3.5 (1.9)	0.469
Smoke exposure (hours per year), n (%)			
<500	5 (26)	5 (13)	0.202
>500	14 (74)	34 (87)	
Burning trash, n (%)			
No	17 (41)	34 (41)	1.000
Yes	24 (59)	48 (59)	
Primary source of light, n (%)			
Kerosene lamps	33 (81)	65 (79)	0.912
Candles	3 (7)	5 (6)	
Electricity	5 (12)	12 (15)	

Abbreviations: SD, standard deviation; IQR, interquartile range.

Factors Associated with COPD

The results of factors associated with COPD explored in the bivariate analysis model are summarized in Table 4. Cases who had a history of physician-diagnosed asthma were six (95% CI 1.21–29.73) times more likely to have COPD compared to gender- and age-matched controls. Cases with a prior history of atopy diagnosis were 3.3 (95% CI 1.39–7.72) times more likely to have COPD compared to controls. Cases who reported a history of smoking were 4.4 (95% CI 1.59–11.99) times more likely to have COPD than their matched controls. Cases who reported a history of TB disease were 5.9 (95% CI 0.62–57.68) times more likely to have COPD compared to controls, but the results did not show statistical significance. A similar trend was seen in cases who were subsistence farmers, those were using kerosene lamps as the primary source of light in their homes, and those who reported firewood use, but there was no proof of statistical significance.

In the multivariate analysis (Table 5), our final model consisted of covariates with a p-value of ≤0.2. Cases who reported a history of smoking were 3.5 (95% CI 1.20–10.10) times more likely to have COPD and those with a history of atopy were 3.0 (95% CI 1.19–7.72) times more likely to have COPD than age- and gender-matched controls. Cases with

Table 4 Results of Bivariate Analysis Showing Risk Factors for COPD

Covariates	Odds Ratio	95% CI	p-Value
Subsistence farming	1.1	0.51–2.42	0.793
HIV positive	0.8	0.48–1.35	0.400
TB disease	5.9	0.62–57.68	0.121
Atopy	3.3	1.39–7.72	0.006
Smoking	4.4	1.59–11.99	0.004
Charcoal use Firewood use	Ref 1.1	 0.39–3.12	 0.860
Not involved in cooking Cooking primary responsibility	Ref 0.8	 0.23–2.61	 0.696
Kitchen smoke: annual exposure hours	0.4	0.06–2.64	0.355
Burning trash	1.0	0.48–2.09	1.000
Electric lamps or candle use Kerosene lamps	Ref 1.7	 0.61–4.52	 0.321

Abbreviations: HIV, human immunodeficiency virus; TB, pulmonary tuberculosis.

Table 5 Results of Multivariate Analysis Showing Risk Factors for COPD

Covariates	Odds Ratio	95% CI	p-Value
Asthma	4	0.72–21.79	0.110
Tuberculosis	5.3	0.43–63.75	0.192
Smoking	3.5	1.20–10.10	0.022
Allergy	3.0	1.19–7.72	0.020

a positive history of asthma and those who reported a history of TB were more likely to have COPD than matched controls, but this result did not show statistical significance.

Discussion

The results of our study suggest that the variables associated with the presence of COPD among participants attending MRRH were a history of having ever smoked and a prior history of atopy. This brings to our attention the fact that smoking remains a major risk factor for COPD in our setting, just as it is in developed countries.

The positive association between COPD and smoking is historical and not surprising, even in our setting. Several other studies have documented an association between smoking and COPD in sub-Saharan Africa. Most of these studies have been cross-sectional in design. The FRESH AIR study, from Uganda, reported similar findings,[13] as did a study conducted in Malawi.[16] A study conducted in Kigali, Rwanda, also found a significant association between COPD and smoking.[17]

Our study found an association between atopy and COPD, which was an interesting one. The association remained statistically significant even in the final multivariate model. Although most literature has stated atopy to be a risk factor for asthma, there is evidence to suggest a high prevalence of atopy in patients with COPD and thus an association between COPD and atopy.[18] In fact, COPD patients with atopy have been found to show greater improvements from using inhaled steroids than those without a history of atopy.[19]

The possibility of other non-traditional factors contributing to the COPD burden in our setting, as we had hypothesized, cannot be ignored. We were, however, not able to prove a statistically significant association between COPD and factors such as asthma history, HIV infection, TB disease history, and biomass exposure. However, there was a trend towards these factors increasing the likelihood of COPD. A study conducted among people living with HIV in south-western Uganda suggested a higher prevalence of COPD in HIV-positive patients and those who had a history of TB, but because of low numbers, it was not powered to measure associations.[20] A systematic review carried out in 2013 also suggested a positive association between TB and COPD.[21]

We had hypothesized a possible association between biomass exposure and COPD; however, we were not able to obtain a statistically significant relationship in our analysis. A previous study conducted in rural Uganda reported high levels of $PM_{2.5}$, which is potentially a surrogate measure for indoor air pollution due to biomass exposure.[22] Whether this exposure to high levels of $PM_{2.5}$ contributes to COPD independently of other exposures is still unknown, and there are ongoing follow-up studies using real time $PM_{2.5}$ monitors that hope to answer this question. A systematic review and meta-analysis in 2009, which involved 23 studies, examined the risk of developing COPD from indoor air pollution, and reported an increased likelihood of COPD from exposure to wood smoke, biomass, or coal.[23] Therefore, although we were not able to find a significant association between biomass exposure and COPD in our study, there is supportive evidence to suggest an association.

Our study has several limitations. It was powered to mainly answer the primary objective, which was the association between smoking and COPD, and this may have limited the power to detect other associations. The sample size was very small because of the nature of cases (rare to find), and the study duration was limited. Since it was a hospital-based case–control study focusing on COPD cases coming to the chest clinic, it is very hard to generalize the findings to the community. Lastly, this being a case–control study, it may be subject to recall bias.

Despite these limitations, our study has an important strength. This is the first hospital-based case–control study investigating COPD risk factors in Uganda. It could lay the groundwork for larger studies to be conducted in similar settings.

Conclusion

Our study has shown that the factors associated with COPD are smoking and a history of atopy. Patients with a history of asthma and tuberculosis are also probably more likely to develop COPD than those without similar disease conditions.

Data Sharing Statement

The datasets used during this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Mbarara University of Science and Technology's faculty review board and institutional ethics review board. Informed written consent was obtained from every participant before recruitment to the study. All methods in this study were carried out in accordance with relevant guidelines and regulations.

Disclosure

The authors declare that they have no competing interests.

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