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ORIGINAL ARTICLE

Occupational emphysema in South African miners at autopsy; 1975–2014

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Abstract

Purpose To determine the associations between exposure duration, measured by employment tenure, and emphysema presence and severity in black and white South African miners at autopsy.

Methods We examined the association between mining tenure and emphysema presence or severity using the Pathology Automation (PATHAUT) database, 1975–2014. We used logistic regression models adjusted for age, tuberculosis, HIV status, and year of death. The effect of smoking on the presence and severity of emphysema was assessed in a sub-analysis of white miners.

Results Mining tenure was significantly associated with increased odds of emphysema presence in black and white miners. For every 10-year increase in tenure, black miners had a 17% increase in odds of emphysema [ORblack = 1.17 (95% CI 1.12, 1.22)] and white miners had a 7% increase in odds of the disease [ORwhite = 1.07 (95% CI 1.04, 1.10)]. Tenure was significantly associated with emphysema severity among black miners [ORseverity = 1.16 (95% CI 1.06, 1.28)]. In a subset of white miners with smoking status, we found that for every 10 years of tenure, there is a significant increase in odds of emphysema presence and severity [ORpresence = 1.14 (95% CI 1.09, 1.19); ORseverity = 1.06 (95% CI 1.00, 1.10)] after adjusting for smoking.

Conclusions We observed a significant relationship between mining tenure and emphysema severity among South African miners in PATHAUT between 1975 and 2014. This relationship was evident in multi-variable analyses adjusted for smoking among white miners. Hazards from long term exposure to inhaled mineral dust leading to lung damage (silicosis, fibrosis, COPD) is evident and warrants further improvement of working conditions and prevention measures in South African mines especially for black workers. Further research is needed to determine if there is an effect of TB and HIV co-infection on the development of emphysema.

Keywords Emphysema · Mining · Occupation · COPD · South Africa · PATHAUT

Background

Emphysema is a major global occupational health concern. Emphysema is one form of chronic obstructive pulmonary disease or COPD. The diagnosis is made when lung pathology shows that the air spaces distal to the terminal bronchiole are enlarged and the surrounding lung is destroyed, without signs of fibrosis or scarring (Berg and Wright 2016). This causes the destruction of lung parenchyma with loss of elasticity leading to obstructive lung disease (Berg and Wright 2016). There is evidence that mineral dust may increase the production of reactive oxygen species (Huang et al. 1993) and enzymes that cause connective tissue breakdown (Zay et al. 1999), leading to emphysema.

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The prevalence and severity of occupational lung disease in miners, including emphysema, is a function of commodity type, intensity of exposure, duration of exposure, and host susceptibility (Ross and Murray 2004). There is evidence to suggest that smoking and mineral dust exposure have an additive effect on the severity of emphysema (Kuempel et al. 2009). Currently, there is no effective prevention for emphysema other than exposure reduction and smoking cessation (Mather et al. 2012).

Emphysema has long been associated with cigarette smoking, however, there is significant evidence to suggest that emphysema can develop as a result of exposure to mineral dust (Kuempel et al. 2009). One review of epidemiological and pathological evidence included three studies of South African gold miners and assessed the exposure–response relationship between silica and emphysema at autopsy. The authors found that working for 20 years in high concentrations of respirable silica increased the risk of emphysema between 3.5 times (95% CI 1.6, 6.6) and 12.7 times (95% CI 3.0, 52.0) in comparison to those with low dust exposure (Hnizdo and Vallyathan 2003). Another study of respiratory outcomes among 725 South African coal miners at autopsy found that emphysema severity was associated with exposure duration (Naidoo et al. 2005).

The association between smoking and emphysema severity is well known. An early study of 1553 South African gold miners at autopsy showed that the mean emphysema severity score (adjusted for the effect of dust, silicosis, and age) was higher in individuals who smoked more than 20 cigarettes per day compared to non-smokers (36.5 versus 7.1, respectively) (Hnizdo et al. 1991). Moreover, age has also been shown to be another risk factor for emphysema; studies have shown that the risk of emphysema increases with age and individuals ≥ 60 years have the highest risk (Halbert et al. 2006; Fukuchi 2009). Tuberculosis (TB) has also been shown to cause chronic impairment of lung function that increases with increasing number of TB exacerbations, longer duration of episodes, and increasing age (Lancaster and Tomashefski 1963; Hnizdo et al. 2000; Ramos et al. 2006; Chakrabarti et al. 2007).

The burden of human immunodeficiency virus (HIV) is a major concern for the sub-Saharan region of Africa for the mining industry where a drastic increase in HIV prevalence was seen in South African gold miners from 0.03% in 1990 to 27% in 2000 (Rees et al. 2010). A cross-sectional study of two adjacent towns in South Africa found that migrant gold miners had a higher prevalence of HIV compared to non-migrant gold miners (25.9 versus 12.7%) (Lurie et al. 2003). Gold mining is not unique in having high HIV prevalence in South Africa, industries that rely on migrant labor such as heavy engineering, metal processing, transportation, and other mining commodities had some of the highest burden that were well above the national average of 18.8% in 2006 (Lurie et al. 2003). Since HIV is associated with COPD, which could be due to emphysema, HIV could be a confounder or effect modifier in the association of mine dust exposure and emphysema.

Emphysema prevalence rates have increased among autopsied South African miners from 250 per 1000 to 355 per 1000 individuals between 2010 and 2013 as reported by the South African National Institute for Occupational Health (NIOH) (2015). Many developing countries, including South Africa, have few resources to implement adequate dust controls and also have informal or non-regulated mines (Ross and Murray 2004). As a result, in South Africa, miners have been exposed to high levels of respirable dust (~0.4 mg/m^3) and dust which in gold mines contains high levels of silica (~30%) (Hnizdo et al. 1994). Furthermore, 40% of black miners who come to autopsy have evidence of active pulmonary tuberculosis (TB) that was not diagnosed during life (Lowe and Murray 1994). This despite official estimates by the mining industry physicians claiming high levels of TB detection and treatment in miners (Stuckler et al. 2013).

Over the last 3 decades, the South African mining workforce has stabilized with less turnover as more black miners work under long-term contracts. Legislation changes post-apartheid also contributed to the work force infrastructure stabilization and increase in tenure among blacks in the mining industry (Murray et al. 2011). Unfortunately, black miners still carry a higher burden of most occupational diseases compared to whites and race remains a significant determinant of occupation, salary, and housing (Murray et al. 2011). The main objective of this observational study was to determine the presence and severity of emphysema in this population and evaluate these findings in relation to race and exposure duration, as measured by mine employment tenure.

Methods

Data source

Subjects in this analysis were from the Pathology Automation (PATHAUT) database from 1975 to 2014. Pathology Automation is a computerized autopsy database that is used for monitoring occupational lung disease trends in the South African mining industry. It is the only comprehensive South African database of occupational lung disease in the mining industry and yearly summary reports are published. The database contains 110,167 deceased miners (as of 2014) with demographic information, occupational history, and information based on lung pathology results and other clinical information. This information is then used to report occupational lung disease trends as well as researching associated causes and risk factors (Hessel et al. 1987a, b).

Autopsies are evaluated by qualified pathologists. South African regulations require physicians to remove cardiopulmonary organs of any individual suspected to have worked in the mines and submit them for examination by NIOH, if next of kin consents (Hessel et al. 1987a, b). Miners who die within 100 km of Johannesburg have the option to send the entire body to NIOH for examination in accordance with the Occupational Disease in Mines and Works Act of 1973 (RSA 1973; Hnizdo et al. 1994). The information derived from autopsy is primarily used to determine eligibility for compensation. Participation in PATHAUT varies by race such that whites are more likely to have whole body versus cardiopulmonary organs. Historically, autopsies for white miners have been arranged by relatives in cooperation with local health care professionals while autopsies of black miners are arranged by the mine medical officer with the consent of the relatives who often reside in remote areas and are difficult to trace (Hessel et al. 1987a, b).

Case definition

This study included individuals who were miners in South Africa. The main outcomes of these analyses were emphysema presence and severity. Emphysema severity was classified using a standardized method by trained pathologists at NIOH in South Africa, into none, insignificant, moderate, or marked in accordance to the percentage of the lung affected by the disease. Emphysema is considered "insignificant" if < 33% of the lungs are involved; "moderate" if 33–66% of the lungs are involved; or "marked" if > 66% of the lungs are involved. An emphysema case was defined as an individual who was found to have insignificant, moderate, or marked emphysema (compared to "absent") by a trained pathologist at autopsy. Emphysema presence was defined as either "present" or "absent" and emphysema severity was defined as "moderate/marked" compared to "absent/ insignificant". PATHAUT does not have estimates of cumulative lifetime dust exposure or composition of the dust, therefore, years of mining tenure was used as a proxy for exposure. Cumulative mining tenure which combines all years worked across various commodities for each miner was used, as most miners changed jobs during their careers either within the mining industry or outside.

Race

Black miners in the South African mining industry have typically been migrant workers (Hessel et al. 1987a, b; Rees et al. 2010; Ndlovu et al. 2016). Once they leave employment, former miners who die at their homes either in South Africa or other neighboring countries have limited access to facilities for organ removal (Hessel et al. 1987; Nelson et al. 2010). Historically black miners were hired under short term contracts and, therefore, had lower average tenure in comparison to white miners (Ndlovu et al. 2016). Segregation laws only allowed black immigrants to have short term work permits (Rees et al. 2010). As a result of the differences between blacks and whites in terms of access to autopsies, historical employment patterns, length of tenure, and other socio-economic differences that have led to racial disparities, separate analyses were performed for each race.

Statistical analysis

The main exposure variable, tenure, was treated as a continuous variable for most analyses, except to examine a dose–response relationship where it was stratified by quartiles. To ensure that the clinical and or theoretical meaning of the regression coefficient for cumulative tenure is clear, we report the effect of tenure in 10-year increments for all logistic regression models. The covariates of interest in this study were age, TB, smoking status, year at death, and HIV status. Age was analyzed as a continuous variable and it was categorized into sextiles by 10-year increments from less than 24 years old to 65 and older for descriptive statistics purposes. Year of death was used to act as a proxy for mining cohorts. Mining practices and access to screening and medical care in the country changed dramatically between 1975 and 2014 because of the political changes. More importantly, access to PATHAUT, screening, medical care and the ability to pay for screening/treatment would be more strongly correlated with the year a miner died than the year the miner was born.

PATHAUT does not have information on previous episodes of TB, therefore, we used active TB status at autopsy dichotomized into present or absent. HIV was dichotomized to present or absent (yes/no), based on HIV status and HIV-related mortality. To compensate for underreporting, we used AIDS-related deaths as a surrogate for HIV status. The AIDS-related causes of death considered were Kaposi's sarcoma, cryptococcal pneumonia, pneumocystis carinii, and cytomegalovirus. Smoking was categorized into current smoker, former smoker, or never smoker.

The distribution of covariates was examined across categories of emphysema presence and severity. Univariate and bivariate analytical methods were employed to determine the association of emphysema presence and severity with risk factors such as age, tenure, TB, year at death, and smoking status. Outlier values for age (higher than the 99th percentile) among black miners (99 years old and older; $n = 69$) and white miners (103 and older; $n = 84$) were excluded from the analysis.

Observations that were missing on any of the outcome measures or covariates were excluded from multivariable models (Fig. 1). Female miners were excluded as they comprised < 0.3% of the observations in PATHAUT. Our

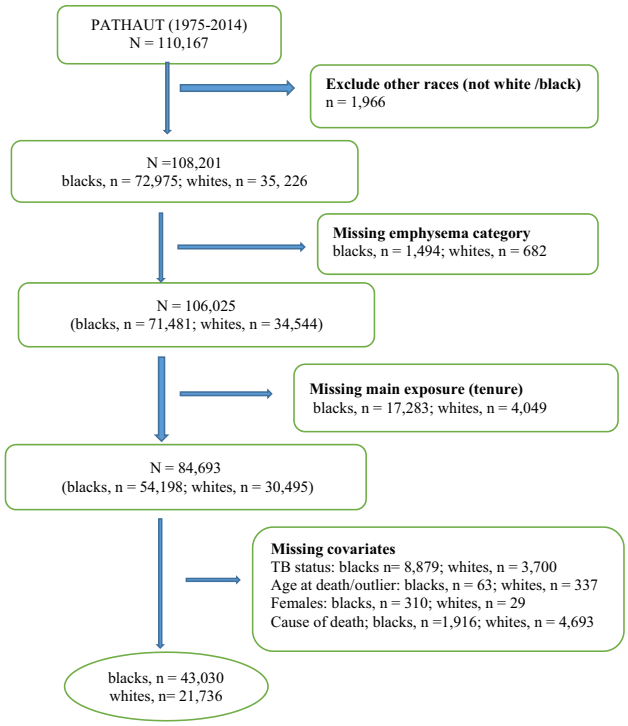

Fig. 1 Inclusion/exclusion criteria for PATHAUT analysis of emphysema presence and severity

outcomes of interest were: (a) presence of emphysema, regardless of severity and (b) cases with severe emphysema (moderate or marked) versus non-severe emphysema (absent or insignificant emphysema).

Crude logistic regression models were built first to evaluate exposure indicators and emphysema presence and severity. Multivariable logistic regression models were then used to assess cumulative tenure association with emphysema adjusting for age at death, HIV, active TB, and year of death in South African miners. Effect modification of select sociodemographic variables (age and race) and risk factors (tenure, smoking, and TB status) were assessed on the multiplicative scale. The Pearson correlation coefficient and the *c*-statistic were used to determine correlation and model fit. Age and total exposure years were relatively correlated in both black and white miners ($r = 0.60$ for blacks and $r = 0.55$ for whites). Since age is independently predictive of emphysema, we kept it in the model. The model fit was also better with age in the model (*c*-statistic = 0.75) that without age (*c*-statistic = 0.64) among black miners. Similar findings were observed in white miners (*c*-statistic = 0.72 with age versus *c*-statistic = 0.66 without age). However, the addition of a collinear variable might lead to underestimation of the association and increase the standard error in our models.

Smoking information was available for 55% of white miners; however, nearly all black miners (99%) were missing smoking information. Therefore, smoking was only included in a sub-analysis of white miners adjusted for age at death, HIV, and year of death. Since none of the white miners in the sub-analysis had TB, it was not included in that sub-analysis. TB and HIV were examined as an effect modifier to discern any possible effect on emphysema severity. Tenure quartiles for each racial group were based on the tenure distribution within each race.

Results

This analysis included 43,030 black and 21,736 white deceased miners in South Africa from 1975 to 2014. Table 1 shows the distribution of emphysema categories by covariates. The mean age at death was 39.2 (STD = 11.3) years among black miners and 61.1 (STD = 14.2) years among whites. Mean mining tenure was 10.1 (STD = 8.2) years among black miners and 24.9 (STD = 12.0) years among white miners. About 12% of blacks ($n = 4961$) and 51% of whites ($n = 11{,}815$) were found to have had some form of emphysema at time of autopsy. Among white miners, 36% of never smokers had some form of emphysema. Gold was the most common commodity mined in PATHAUT (~ 70%), regardless of race.

Crude associations between each covariate and emphysema presence and severity are shown in Table 2. Among black miners, emphysema presence increased with increasing tenure with the highest tenure quartile (15.4–50.0 years) being associated with more than a threefold increase in odds of emphysema presence [OR = 3.48 (95% CI 3.18, 3.81)] and severity [OR = 3.67 (95% CI 2.79, 4.81)] compared to those in the lowest tenure quartile (0.1–3.2 years). TB was associated with increased odds of the presence of emphysema among black miners only [OR = 1.14 (95% CI 1.04, 1.25)].

Among white miners, tenure was significantly associated with emphysema presence and severity with the highest quartile (34.1–50.0 years) being associated with more than a threefold increase in odds of emphysema presence [OR = 3.36 (95% CI 3.11, 3.64)] and a more than twofold increase in emphysema severity [OR = 2.39 (95% CI 2.14, 2.69)] compared to individuals in the lowest tenure quartile (0.1–15.9 years). As expected, age groups 35 years and older were significantly associated with both the presence and severity of emphysema when compared to miners younger than 24 years old (Table 2). The odds of emphysema presence and severity increased with increasing age at time of autopsy.

Among black miners, the odds of the presence and severity of emphysema increased with the recency of the year of death [$OR_{Presence} = 1.02$ (95% CI 1.01, 1.02) and $OR_{Severity} = 1.01$ (95% CI 1.00, 1.02)]. However, there was no association between year of death and emphysema among white miners.

Table 1 Distribution of emphysema across covariates in South African miners at autopsy, PATHAUT; 1975–2014

	Black miners ($N=43,030$)					White miners ($N=21,763$)			
	Absent, *n* (%)	Insignificant, *n* (%)	Moderate, *n* (%)	Marked, *n* (%)		Absent, *n* (%)	Insignificant, *n* (%)	Moderate, *n* (%)	Marked, *n* (%)
N	38,136 (88.6)	4356 (10.1)	503 (1.2)	35 (0.1)		10,697 (49.1)	7598 (34.9)	3061 (14.1)	407 (1.9)
Age category (years) [mean (STD)] = [39.2 (11.3)]					Age category (years) [mean (STD)] = [61.1 (14.2)]				
< 24	4067 (10.7)	46 (1.1)	1 (0.2)	0 (0.0)	< 24	263 (2.5)	2 (0.0)	1(0.0)	0 (0.0)
25–34	11,420 (29.9)	392 (9.0)	12 (2.4)	1 (2.9)	25–34	849 (7.9)	35 (0.5)	1 (0.0)	0 (0.0)
35–44	11,740 (30.8)	1214 (27.9)	84 (16.7)	5 (14.3)	35–44	1311 (12.3)	258 (3.4)	19 (0.6)	1 (0.2)
45–54	8215 (21.5)	1745 (40.1)	198 (39.4)	10 (28.6)	45–54	1990 (18.6)	1113 (14.7)	232 (7.6)	17 (4.2)
55–64	2257 (5.9)	748 (17.2)	156 (31.0)	7 (20.0)	55–64	2403 (22.5)	2210 (29.1)	889 (29.0)	126 (29.3)
≥ 65	437 (1.2)	211 (4.8)	52 (10.3)	12 (34.3)	≥ 65	3881 (36.3)	3980 (52.4)	1919 (62.7)	283 (65.8)
Tenure quartiles (years) [mean (STD)] = [10.1 (8.2)]					Tenure quartiles (years) [mean (STD)] = [24.9 (12.0)]				
0.1–3.2	10,209 (26.8)	624 (14.3)	59 (11.7)	8 (22.9)	0.1–15.9	3567 (33.4)	1296 (17.1)	475 (15.5)	67 (16.5)
3.3–8.1	9711 (25.5)	842 (19.3)	90 (17.8)	4 (11.4)	16–26.3	2761 (25.8)	1872 (24.7)	707 (23.1)	108 (26.5)
8.2–15.3	9490 (24.9)	1074 (24.7)	133 (26.4)	5 (14.3)	26.4–34.2	2384 (22.3)	2115 (27.1)	848 (27.7)	120 (29.5)
15.4–50.0	8726 (22.9)	1816 (41.7)	221 (43.9)	18 (51.4)	34.3–50.0	1982 (18.5)	2295 (30.3)	1027 (33.6)	112 (27.5)
Tuberculosis					Tuberculosis				
Absent	33,969 (89.1)	3800 (87.2)	463 (92.0)	32 (91.4)	Absent	10,503 (98.2)	7489 (98.6)	3015 (98.5)	401 (98.5)
Present	4167 (10.9)	556 (12.8)	40 (8.0)	3 (8.6)	Present	194 (1.8)	109 (1.4)	46 (1.5)	6 (1.5)
HIV					HIV				
No	32,553 (85.4)	3755 (86.2)	463 (92.0)	34 (97.1)	No	10,650 (99.6)	7489 (99.9)	3054 (99.8)	404 (99.3)
Yes	5583 (14.6)	601 (13.8)	40 (8.0)	1 (2.9)	Yes	47 (0.4)	11 (0.1)	7 (0.2)	3 (0.7)
					Smoking				
					Smoker	2936 (56.6)	2879 (62.1)	1250 (66.3)	119 (59.8)
					Former smoker	1193 (23.0)	1267 (27.4)	534 (28.3)	75 (37.7)
					Never smoker	1056 (20.4)	487 (10.5)	102 (5.4)	5 (2.5)
					Missing ($n=9860$)				

Based on percentage of the lung affected, emphysema was classified into absent, insignificant (< 33%), moderate (33–66%), and marked (> 66%)

In crude models, for every 10-year increase in tenure, black miners had a 75% increase in odds of the presence of emphysema and an 81% increase in odds of a severe case of emphysema while white miners had a 4% increase in the odds of the presence of emphysema and 32% increased odds of a severe case of emphysema (Table 3). In fully adjusted models (adjusted for age at death, comorbidities of HIV and TB, and year of death), black miners had significantly higher odds of both having emphysema [OR = 1.18 (95% CI 1.13, 1.23)] and having severe emphysema [OR = 1.16 (95% CI 1.05, 1.28)] with every 10-year increase in tenure (Table 3, model 1).

Among white miners, the odds of having emphysema at time of autopsy increased significantly with every 10-year increase in tenure [OR = 1.08 (95% CI 1.04, 1.11)], but there was no significant association between mining tenure and emphysema severity. There was a significant dose–response (p trend < 0.001) with increasing tenure and emphysema presence among black and white miners. Among black miners, those who had worked for more than 15 years (highest tenure quartile) were associated with a 51% increased odds of emphysema presence compared to those who have worked for 3 years or less (lowest tenure quartile). White miners who worked for more than 34 years had a 22% increase in odds of the presence of emphysema compared to those who worked for less than 16 years.

Only black miners showed a dose–response association of tenure with emphysema severity (p trend = 0.0007).

Table 2 Associations of covariates with emphysema presence and severity in South African miners at autopsy, PATHAUT, 1975–2014

	Black miners ($N=43,030$)					White miners ($N=21,763$)			
	Emphysema presence		Emphysema severity[a]			Emphysema presence		Emphysema severity[a]	
	OR	(95% CI)	OR	(95% CI)		OR	(95% CI)	OR	(95% CI)
Age category					Age category				
<24	Ref		Ref		<24	Ref		Ref	
25–34	3.07	(2.26, 4.16)	4.51	(0.59, 34.36)	25–34	3.72	(1.14, 12.17)	0.30	(0.02, 4.81)
35–44	9.60	(7.16, 12.88)	28.15	(3.94, 201.38)	35–44	18.59	(5.91, 58.43)	3.38	(0.45, 25.28)
45–54	20.57	(15.37, 27.54)	85.57	(12.04, 608.31)	45–54	59.99	(19.19, 187.60)	21.27	(2.97, 152.16)
55–64	34.93	(25.93, 47.03)	222.26	(31.22, 997)	55–64	117.42	(37.59, 366.86)	57.96	(8.13, 413.15)
≥65	54.45	(39.35, 75.34)	404.70	(56.25, 999)	≥65	139.31	(44.61, 435.02)	73.76	(10.35, 525.86)
Tenure quartiles (years)					Tenure quartiles (years)				
0.1–3.2	Ref		Ref		0.1–15.9	Ref		Ref	
3.3–8.1	1.42	(1.29, 1.58)	1.44	(1.05, 1.97)	16–26.3	1.89	(1.75, 2.04)	1.58	(1.41, 1.77)
8.2–15.3	1.89	(1.71, 2.08)	2.11	(1.58, 2.83)	26.4–34.2	2.51	(2.32, 2.71)	1.93	(1.73, 2.16)
15.4–50.0	3.48	(3.18, 3.81)	3.67	(2.79, 4.81)	34.3–50.0	3.36	(3.11, 3.64)	2.39	(2.14, 2.67)
Tuberculosis					Tuberculosis				
Absent	Ref		Ref		Absent	Ref		Ref	
Present	1.14	(1.04, 1.25)	0.70	(0.51, 0.95)	Present	0.80	(0.65, 0.99)	0.90	(0.67, 1.22)
HIV					HIV				
No	Ref		Ref		No	Ref		Ref	
Yes	0.88	(0.81, 0.96)	0.48	(0.35, 0.67)	Yes	0.43	(0.26, 0.72)	0.91	(0.47, 1.79)
Death year[b]	1.02	(1.01, 1.02)	1.01	(1.00, 1.02)	Death year	0.97	(0.97, 0.97)	0.98	(0.98, 0.99)
					Smoking				
					Never smoker	Ref		Ref	
					Smoker	2.57	(2.30, 2.87)	3.40	(2.77, 4.17)
					Former smoker	2.80	(2.47, 3.17)	3.57	(2.88, 4.43)

[a]Emphysema severity = "moderate/marked" compared to "absent/insignificant" emphysema

[b]Continuous death year

Black miners in the highest quartile had a 57% increase in odds of severe emphysema compared to those in the lowest quartile. There was no significant effect of HIV/TB co-infection on the odds of emphysema presence and severity in the study (results not shown).

We conducted a sensitivity analysis of mining tenure and emphysema presence and severity among white miners with smoking data ($n=11,883$). The models controlled for the same covariates discussed above, except for TB, as no white miners had TB. These models showed an association between each 10-years of mining tenure and emphysema presence [OR = 1.14 (95% CI 1.09, 1.19)] with a significant dose–response (p trend = 0.0006) and emphysema severity [OR = 1.06 (95% CI 1.00, 1.11)] after adjusting for smoking status, age, HIV, and death year (Table 3, Model 3). Moreover, it is important to note that over 35.8% of white miners who were never smokers had some form of emphysema in this study.

Discussion

In an analysis of mining tenure and emphysema, our results show that the odds of the presence of emphysema increased with mining tenure among both black and white miners. However, the odds of severe cases of emphysema only increased significantly per 10-years of tenure among black miners. This difference may be attributable, in part, to the differences in employment patterns between the two races in the mining industry. Black miners have historically had shorter employment tenures, but a larger proportion of black miners were employed in high risk and high exposure jobs, and ultimately dying younger compared to white miners (Nelson et al. 2010). In our analysis, the highest proportion of individuals with moderate or marked emphysema among blacks was within the 45–54 years old age group compared to the ≥65 years old age group among

Table 3 Association between mining tenure and emphysema presence and severity at autopsy among South African miners; PATHAUT, 1975–2014

	Black miners						White miners				
	Emphysema Presence		Emphysema Severity[a]		*N*		Emphysema Presence		Emphysema Severity[a]		*N*
	OR	(95% CI)	OR	(95% CI)			OR	(95% CI)	OR	(95% CI)	
Crude	1.75	(1.69, 1.81)	1.81	(1.66, 1.97)	43,030		1.49	(1.45, 1.53)	1.32	(1.28, 1.36)	21,736
Model 1	1.18	(1.13, 1.23)	1.16	(1.05, 1.28)	43,030		1.08	(1.04, 1.11)	1.01	(0.97, 1.05)	21,736
Model 2		–		–			1.09	(1.05, 1.14)	1.03	(0.98, 1.09)	11,883
Model 3		–		–			1.14	(1.09, 1.19)	1.06	(1.00, 1.11)	11,883
Quartiles[b]					43,030	Quartiles[b]					21,736
0.1–3.2	Ref		Ref			0.1–15.9	Ref		Ref		
3.3–8.1	1.13	(1.02, 1.26)	1.14	(0.83, 1.57)		16–26.3	1.29	(1.18, 1.40)	1.13	(1.00, 1.28)	
8.2–15.3	1.15	(1.04, 1.28)	1.30	(0.96, 1.75)		26.4–34.2	1.30	(1.19, 1.42)	1.11	(0.99, 1.25)	
15.4–50.0	1.51	(1.35, 1.68)	1.57	(1.17, 2.10)		34.3–50.0	1.22	(1.11, 1.34)	1.07	(0.94, 1.21)	
	p trend < 0.0001		p trend = 0.0007				p trend = 0.0002		p trend = 0.6106		

All odds rations (ORs) are scaled to represent cumulative exposure to 10 years of tenure

Model 1: Adjusted for TB (present/absent), HIV (present/absent), death year (continuous), and age (continuous)

Model 2: Sub-analysis of individuals with smoking information; adjusted for HIV (present/absent), death year (continuous), and age (continuous)

Model 3: Sub-analysis of individuals with smoking information; adjusted for smoking status (never smoker/ex-smoker/current smoker), HIV (present/absent), death year (continuous), and age (continuous)

"–"Indicates where smoking-adjusted models were not possible due to poor smoking ascertainment among black miners

[a]Emphysema severity defined as "moderate/marked" compared to "absent/insignificant" emphysema

[b]Tenure quartile models were adjusted for TB (present/absent), HIV (present/absent), death year (continuous), and age (continuous)

white miners. As a result, fully adjusted models show the disparity in exposure duration among black miners. The difference in the duration of exposure was also evident when comparing the mean cumulative tenure between the two groups; on average, black miners had worked for 10 years while white miners worked for 25 years.

One reason we performed separate analysis for each racial group were the disparities in cumulative tenure (mean: 10.1 years for blacks versus 24.9 years for whites) and age at death between black and white miners. As a result, separate tenure quartiles were used based on the cumulative tenure distribution in each race. If we were to use the same quartile range for black miners and white miners, it would have led to drastically unbalanced numbers in each quartile among black miners (only 25% of black miners had tenure ranging from 15.4 to 50 years, $N = 10{,}781$). The significance of still finding an association between exposure in terms of tenure and emphysema in black miners is indicative of the extent of dust exposure in black miners.

Our findings are similar to other studies which have confirmed a relationship between occupational exposure to mineral dust and the development of emphysema. A study of 616 autopsied U.S. coal miners, of whom 183 were non-white, found that race, age at death, and cigarette smoking were significantly associated and additive predictors of emphysema severity (Kuempel et al. 2009). In our study, the association of exposure duration and emphysema persisted even after adjusting for smoking in a sub-analysis of white miners as well as in the subgroup of non-smoking white miners.

Naidoo et al. (2005) found that exposure duration was associated with moderate to marked emphysema in South African coal miners. They noted that individuals with high exposure duration had increased odds of emphysema compared to the low exposure duration group [OR = 3.4 (95% CI 1.9, 5.9)]. Our study, which included all commodities, compared individuals in the highest exposure quartile to those in the lowest quartile, and found a 7% increase in odds of emphysema severity (moderate and marked emphysema) among white miners and a 57% increase in odds of emphysema severity among black miners. Of note, a previous study examining respiratory outcomes at autopsy in South African coal miners (PATHAUT 1975–1997), found the prevalence of emphysema was significantly greater in white miners (16.7%) than black miners (3.1%) (Naidoo et al. 2005). Similarly, in our analysis from 1975 to 2014, we found that the prevalence of emphysema was higher among white miners (50.7%) compared to black miners (11.5%).

There are no good studies of emphysema prevalence in the general South African population, however, there is some data on the broader category of Chronic Obstructive Pulmonary Disease (COPD) in the region. The prevalence of emphysema among white miners is higher than the estimated population prevalence of COPD reported from the Global Initiative for Chronic Obstructive Lung Disease (GOLD). They found a prevalence of 22.2% for men in a community with a high rate of smoking, in Cape Town, South Africa (Buist et al. 2007). In another Cape town study of never smokers, the overall prevalence of COPD was 7.3 and 4.2% of men between the ages of 40 and 49 years had COPD (Lamprecht et al. 2011). Moreover, a meta-analysis of nine cross-sectional studies in Sub-Sahara Africa also reported a prevalence of COPD ranging from 4.1 to 24.8% (Finney et al. 2013).

We also found that the odds of severe emphysema (moderate and marked emphysema) were significantly greater among black miners (16%). This is of great concern given that black miners have historically tended to have shorter tenure and die younger compared to white miners (Nelson et al. 2010). Black miners were historically exposed to significantly higher dust levels such that even if they had relatively shorter tenure and tended to have low average age at death (39.2, STD = 11.3), they were still presenting with emphysema at autopsy.

Age and tenure are often correlated in occupational studies, and controlling for both in epidemiologic studies can introduce collinearity into regression models, thereby producing imprecise estimates of effect. A study of respiratory outcomes among South African coal miners at autopsy using PATHAUT showed evidence that regression models unadjusted for age overestimated the effect estimates for emphysema. Even though age and exposure were significantly correlated in the study ($r = 0.68$; $p < 0.0001$) (Naidoo et al. 2005). In our study, age was not correlated with tenure in fully adjusted models. Furthermore, we observed that age confounded the relationship between exposure duration and emphysema based on a change in parameter estimates of $> 10\%$, whereby models not adjusted for age overestimated the association (results not shown).

Limitations

One of the main limitations of PATHAUT is that participation is voluntary serving as a means for the families of mine workers to obtain compensation. In addition, individuals who are fully compensated while alive may be less likely to present at autopsy. We do not have data about miners who do not submit their organs to the NIOH, therefore, individuals captured within PATHAUT may not be representative of all miners in South Africa. As a result, unbiased prevalence rates of emphysema in South African miners at autopsy cannot be directly estimated from the PATHAUT database. To discern the impact of subjects with missing data, we examined whether the individuals included in the study were significantly different from those who were excluded. Individuals missing data were similar in their distribution of the presence of

emphysema compared to those included in the study. The mean age among black miners excluded from analysis was slightly higher than those included in the study (39 versus 36 years).

Since the diagnosis of emphysema is largely on non-inflated lungs, it is expected that non-differential misclassification might occur leading to an underestimation of the severity of emphysema (Naidoo et al. 2005). In multivariable logistic regression models, emphysema was dichotomized in two ways to assess the extent of this bias and to determine the true importance of emphysema as an outcome variable.

A significant limitation of this analysis was that we lacked smoking data for over 70% of the study sample including nearly all (> 99%) black miners. Smoking data were unavailable for several reasons. In the early years of PATHAUT, the records of white miners have tended to be more complete than those of black miners (Hessel et al. 1987a, b). In addition, the new NIOH autopsy forms introduced in 1996 did not include smoking information. We addressed this limitation by performing a sensitivity analysis of white miners with smoking information. This analysis showed that exposure duration and emphysema association persisted even after adjusting for smoking.

According to the World Health Organization (WHO), the prevalence of smoking in South African males aged 15 years and older in 2015 was 31.4%; a slight decrease from the 34.6% prevalence estimate of year 2000 (World Health Organization 2015). South African blacks, have historically had the lowest smoking prevalence; in 1993, the smoking prevalence among blacks was 28% and by 2003 it had decreased to 20% (van Walbeek 2002). Based on the first South African National Health and Nutrition Examination Survey (SANHANES) conducted in 2012, the prevalence of smoking in South Africa among adults age 18 years and older was 18% with 16% being daily smokers (Reddy et al. 2015). The prevalence of smoking among blacks and whites was 15% with black/mixed-race South Africans having the highest prevalence (40%) (Reddy et al. 2015). These relatively low smoking rates among blacks, and the low likelihood that smoking rates would have been associated with tenure makes us believe that our findings of a significant association between tenure and the presence and severity of emphysema in black workers are of importance.

Moreover, the use of total mining tenure, including work done mining different commodities, as a proxy for exposure was a significant limitation. We did not have exposure measurements, specific data on occupation, proximity to the mining face, or whether the miner worked on the surface or underground. There also was no data on other non-mining dusty jobs or environmental exposures such as use of biomass fuel which may have led to underestimation or overestimations of the effect of mining dust on emphysema in South Africa.

Furthermore, age as a very strong risk factor for emphysema and it is highly associated with mining tenure. As a result, there may be interaction between age and mining tenure that affected the occurrence of emphysema and potentially leading to underestimation of the association. Given these limitations, it was interesting that total mining tenure still showed a relationship to emphysema.

Conclusion

We observed a significant relationship between mining tenure and emphysema severity among South African miners in PATHAUT between 1975 and 2014. This relationship was evident in multi-variable analyses adjusted for smoking among white miners. Hazards from long term exposure to inhaled mineral dust leading to lung damage (silicosis, fibrosis, COPD) is evident and warrants further improvement of working conditions and prevention measures in South African mines especially for black workers. Further research is needed to determine if there is an effect of TB and HIV co-infection on the development of emphysema.

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Compliance with ethical standards

Conflict of interest All authors have declared that they have no conflicts of interest that may be relevant to the submitted work.

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