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ORIGINAL ARTICLE

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Correlation between autopsy findings for chronic obstructive airways disease and in-life disability in South African gold miners

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Abstract ***Objectives:*** In South Africa chronic obstructive airway disease (COAD), which could be due to working in a dusty atmosphere in scheduled mines or works, is a compensatable disease. Miners are compensated for in-life respiratory disability and for findings at autopsy of COAD, which includes emphysema, bronchitis assessed by mucus gland hyperplasia in the main bronchus, and bronchiolitis assessed by goblet cell metaplasia. The question arises as to whether the autopsy findings correlate with in-life impairment. The objectives of the study were: (1) to determine whether autopsy COAD outcomes relate to lung function and to respiratory symptoms and signs; and (2) to quantify the individual contributions of emphysema, bronchiolitis and bronchitis to lung function impairment. ***Methods:*** On 724 gold miners, pathological findings of COAD – emphysema, bronchitis and bronchiolitis – were related to lung function measurements and respiratory symptoms and signs observed within 5 years prior to death. ***Results:*** Emphysema diagnosed at autopsy was the main determinant of airflow impairment. The emphysema score categories 0–5, 5–35, 35–65 and >65 were associated with decreased forced expiratory volume in 1 s, expressed as percentage predicted (FEV_1%) as follows: 78.8%, 66.2%, 52.0% and 46.0%, respectively. The score was also associated with increasing frequency of dyspnoea. After adjustment for emphysema, the bronchitis and bronchiolitis were not related to significant lung function loss, and in subjects without emphysema, the presence of moderate or marked bronchitis was associated with a mild impairment only. Bronchitis at autopsy was associated with increased frequency of rhonchi, sputum and cough, whereas bronchiolitis was associated with increased sputum only. Silicosis found at autopsy was associated with some obstructive and restrictive lung function impairment. Tobacco smoking was associated with all the COAD outcomes.

Key words Clinico-pathological correlations · Lung function · Emphysema · Bronchitis · Bronchiolitis · Silica dust

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Introduction

Epidemiologic studies on South African gold miners have shown that silica dust exposure and silicosis are risk factors for lung function impairment, and for mortality from chronic obstructive airway disease (COAD) (Wiles and Faure 1977; Cowie and Mabena 1991; Hnizdo 1992; Trapido et al. 1998). Since 1973, COAD which could be due to working in a dusty atmosphere in scheduled mines or works has been a compensatable disease. COAD is progressive, and respiratory disability due to dust often develops after cessation of dust exposure. Because many miners do not have medical follow-up after the end of their employment, current legislation allows for financial compensation based on autopsy results. Deceased miners with adequate service, who had a moderate or marked degree of emphysema, bronchiolitis, or bronchitis diagnosed at autopsy, are eligible. The question arose as to whether the autopsy COAD-assessment correlates with lung function abnormalities in life.

According to American Thoracic Society standards (ATS 1987), COAD is characterised by abnormal expiratory airflow that does not change markedly over

several months of observation. Three disorders are incorporated in COAD: emphysema, peripheral airway disease, and chronic bronchitis. Emphysema is characterised by abnormal, permanent enlargement of the airspaces distal to the terminal bronchiole, with destruction of their walls, and is assessed morphologically at autopsy. Peripheral airways disease includes pathological features such as inflammation of the terminal and respiratory bronchioles, fibrosis of airway walls with narrowing, and goblet cell metaplasia of the bronchiolar epithelium. Correlations suggest that small airway disease contributes to airflow obstruction, but that its importance on lung function is secondary to that of emphysema. Chronic bronchitis refers to "the condition of subjects with chronic or recurrent excess mucus secretion into the bronchial tree".

The compensation criteria for COAD in gold miners are based on functional disability in life and on autopsy findings, provided that there has been a minimum of 10 years service in conditions of high dust, or of 13 years in low dust. Smoking history is not taken into consideration. In life, COAD first degree is assigned for moderate impairment of lung function and second degree for severe impairment. Pulmonary impairment is graded according to percent of predicted value for one second forced expiratory volume (FEV_1), forced vital capacity (FVC) and the observed FEV_1/FVC ratio, respectively, as follows: normal (≥80%, ≥80%, ≥75%), mildly impaired (79–65%, 79–65%, 74–65%), moderately impaired (65–52%, 65–52%, <65%), severely impaired (<51%, <55%, <55%). At autopsy, emphysema is graded by a score ranging from 0 to 100. COAD first degree is assigned for moderate emphysema, (score 35–64), and second degree for marked emphysema (score 65). Bronchitis is assessed as the amount of mucus gland hyperplasia in a main bronchus, graded by the Reid index (Gough and Wentworth 1960). COAD first degree is assigned for moderate bronchitis (Reid index = 0.6–0.7), and second degree for marked bronchitis (Reid index >0.7). Bronchiolitis is assessed by the presence of goblet cell metaplasia in the bronchioles. COAD first degree is assigned when 50–75% of bronchioles are involved, and second degree is assigned when over 75% are involved.

The main objective of the study was: (1) to determine how the pathological diagnosis of COAD correlates with clinical observations (chiefly lung function tests and recorded respiratory symptoms and signs), and (2) to quantify the individual contributions of emphysema, bronchiolitis and bronchitis to lung function impairment in life. The results are discussed in relation to current compensation policies.

Material and methods

Selection of study subjects

By South African law, autopsy of the heart and lungs is required for all miners and ex-miners on death, provided that the next of kin agrees. For subjects who died within 100 km of Johannesburg, a full autopsy is offered. For those who died further afield, the organs are removed locally, preserved in formalin and sent to the National Centre for Occupational Health (NCOH) in Johannesburg. Autopsies are performed by pathologists at the NCOH according to a standard procedure, and the results are sent to the Medical Bureau for Occupational Disease (MBOD) for determination of the amount of compensation. Since 1974, autopsy results have been computerised on a database called PATHAUT (Hessel et al. 1987).

Study subjects were selected from the PATHAUT database if they fulfilled the following criteria: (1) autopsy performed between 1975 and 1986; (2) 80% of mining service in gold mines; (3) less than 1 year asbestos mining; (4) lungs inflated at autopsy; (5) tissue adequately preserved to enable histological assessment of bronchiolitis and bronchitis; (6) lung function tests undergone within 5 years of death. Results of lung function tests carried out 5 years before death were available mainly from white miners, and 85% of white miners have an autopsy, thus only white miners were included in the study. There were 8,462 people who satisfied conditions 1–4. Of these, 2,427 did not have adequately preserved tissue to satisfy criterion 5, leaving 6,035 who fulfilled criteria 1–5. These miners were classified into 8 categories according to all possible combinations for the presence or absence of emphysema, bronchitis, or bronchiolitis. There were 3,384 miners who did not have any, or had minimal, pathological findings of COAD; a sample of 500 of these people was selected for the study. The remaining 2,651 fell into the other 7 categories. From the 3,151 (500 + 2,651) miners, we excluded those who had not had lung function tests within 5 years prior to death, and also cases of cardiac failure, leaving 724 people in the study. At the time when the subjects underwent lung function investigation, the tests were done mainly on those requesting compensation, or on those presenting with medical problems. The above selection procedure was designed to obtain good quality autopsy and lung function data, but it did not necessarily result in a representative sample of miners.

Autopsy

The presence of compensatable disease is established by macro- and microscopic examination of the lungs.

Emphysema

At autopsy, emphysema is assessed on all lungs; however, for the present study only men who have had a full autopsy were eligible. This is because whole-lung sections, which are required for meticulous assessment of emphysema, must be prepared from lungs which are inflated when removed from the thorax. The lungs are expanded with formaldehyde, and a paper mounted whole-lung section is made from one lung, with the Gough-Wentworth technique (Gough and Wentworth 1960). Emphysema is graded by a score between 0 and 100. The degree of emphysema is categorised as absent (<10), insignificant (10–34), moderate (35–64), and marked (≥65). To obtain exact emphysema scores for the study subjects, we requested that the whole-lung sections be reassessed and scored by Dr. B. Goldstein from the NCOH.

Bronchitis

Bronchitis is assessed by mucus gland hyperplasia in a main bronchus. It is categorised according to the ratio of the thickness of the mucous gland layer to the thickness of the wall between the epithelium and the cartilage (i.e., the Reid Index), as absent, insignificant (<0.6), moderate (0.6–0.7), and marked (>0.7).

Bronchiolitis

Bronchiolitis in small airways (<2 mm diameter), is assessed mainly by goblet cell metaplasia. Bronchiolitis is graded by the

ratio between the number of goblet cells and the total number of cells seen, as absent, insignificant (up to 50%), moderate (50–75%), and marked (> 75%).

Because the lungs are already in varying stages of decomposition when preserved in formalin, the assessment of airways disease is compromised. This is particularly so for small airways, as often only small, loose pieces of bronchiolar epithelium can be seen. This study used only cases that showed adequate tissue preservation, which was indicated by the computerised records.

Silicosis

Silicosis is graded, according to the number of palpable silicotic nodules, as absent, insignificant (< 5 nodules), slight (5–14 nodules), moderate (15–30 nodules) and marked (> 30 nodules). The presence of silicosis is confirmed by histological examination.

All information on pathological findings was extracted from the PATHAUT database, except for the emphysema score, which was re-assessed for this study.

Clinical findings and lung function tests

For each eligible study subject, we extracted from the MBOD medical files the results of lung function tests done within 5 years prior to death, and information on respiratory symptoms and signs.

Lung function measurements

The MBOD has a well-equipped lung function testing laboratory with trained and experienced technicians. Spirometry was performed by Godart water sealed spirometers using methods in reasonable accord with recommendations published by the ATS (ATS 1979; Irwig 1986). The same instruments were used during the study period. The spirometers were of 9 l capacity with breathing resistance of approximately 4 mm H20 at 100 l/min. They were checked daily for leaks, and monthly for the accuracy of time and volume measurements. The subjects were seated during the test, and a rubber mouthpiece and noseclip were used to avoid leakage of air. Three acceptable tracings were obtained, where the criteria for acceptance were maximum effort, a smooth expiratory curve, and a prompt initiation. The highest lung function values were recorded. The functional residual capacity was measured by a plethysmograph, to obtain total lung capacity (TLC). The tests used for the study were FEV_1, FVC, and FEV_1/FVC, expressed as percentage predicted FEV_1%, FVC%, FEV_1/FVC%, and the observed data for TLC and forced mid-expiratory flow ($FEF_{25–75\%}$). Each individual's height, age and weight at the time of testing were recorded. Percentages of predicted values were obtained directly from the lung function records.

Clinical data

Data on respiratory symptoms (dyspnoea, sputum and cough) and signs (rhonchi) were obtained from the medical examination at which lung function was assessed. The periodic medical examinations routinely included standard questions on cough, sputum and dyspnoea, but these were not asked in a standard epidemiologic format to establish the presence of chronic bronchitis.

Silica dust exposure

A complete work history for each miner was extracted from the Chamber of Mines' personal records. These accurately register the number of shifts worked in each mine and the miner's occupation. During the 1960s, a study done by Beadle (1971) estimated the average dust exposure, in terms of respirable surface area (RSA), for occupational categories in South African gold mines. Cumulative dust exposure (CDE) total, and up to the age of 50, in RSA-years units was calculated by weighting the number of shift-spend in each occupational class by Beadle's average dust measurements for occupational categories (see Wiles and Faure 1977). Most miners retire at approximately 50 years of age.

Smoking history

Smoking history was obtained from the MBOD medical files. Smoking habits have been recorded at each periodic examination since 1960. The number of cigarettes per day was averaged over the working life and multiplied by years of smoking to get tobacco pack-years.

Statistical analysis

Analysis of lung function and clinical findings

To establish the reliability of in-life symptoms and signs, we first assessed the associations between these and the known risk factors (smoking, dust and age). The relationship was measured by the adjusted odds ratio, estimated in the logistic regression (SAS 1988; PROC LOGIST). Next, we determined the association between respiratory symptoms and signs, and lung function. The mean lung function values for increasing severity of symptoms were calculated and a test for trend performed by regression analysis. To determine which of the respiratory symptoms and signs best related to lung function, we applied the linear regression model, which included all the symptoms and signs, and height, weight, age, pack-years of tobacco smoking and dust exposure.

Relationship between in-life and autopsy findings

The analysis of variance and multiple comparison tests were used to investigate whether the severity of autopsy findings is associated with increasing lung function impairment. The lowest severity category was used as a comparison group in the multiple comparisons of the means. The association between the severity of autopsy findings and the presence of symptoms and signs in life was assessed by the chi-square test for trend. Risk factors for emphysema, bronchitis, bronchiolitis, and silicosis were identified by logistic regression. To determine which of the pathological findings are most strongly associated with lung function, we applied the stepwise linear regression model.

Results

There were 724 subjects who fulfilled the selection criteria. Lung function tests were invalid in 21 miners, thus only 703 were analysed for lung function. Table 1 summarises the characteristics of the subjects. On average, they were 64.2 years old at death and the mean duration of service was 23.7 years. A large percentage of the miners had respiratory symptoms and signs.

Validity of clinical findings

The association between clinical findings and increasing categories of smoking and CDE was evaluated by multivariate logistic regression. All clinical findings for COAD were associated with smoking, and only dyspnoea and rhonchi showed some tendency for an association with dust. Of the outcomes, rhonchi showed the

Table 1 Characteristics of the study population (*CDE* cumulative dust exposure, *RSA* respirable surface area, FEV_1 one second forced expiratory volume, *FVC* forced vital capacity, $FEF_{25-75\%}$ forced mid-expiratory flow)

Characteristic	*n*	Mean (SD)	Range
General			
Year of birth	724	1916 (8.6)	1880–1945
Age at death (years)	724	64.2 (8.3)	38–102
Smoking history			
Pack-years smoked	724	31.8 (21.1)	0–119
Work history			
CDE by 50 years (RSA-years/1,000)	724	23.30 (14.10)	0–67.84
Total CDE (RSA-years/1,000)	724	28.56 (17.49)	0–96.15
Years of gold mining dust exposure	706	23.7 (18.0)	0.1–44.7
Lung function			
Age at lung function test (years)	703[a]	61.5 (8.3)	35–99
Years prior to death	703	2.2 (1.5)	0–7[b]
FEV_1 (% predicted)	703	65.3 (22.4)	13.0–130.0
FVC (% predicted)	703	83.4 (16.6)	39.0–150.0
FEV_1/FVC (% predicted)	703	60.9 (15.6)	18.1–109.8
$FEF_{25-75\%}$	703	1.53 (1.14)	0.14–7.30
Total lung capacity (l)	524	7.10 (1.23)	3.72–12.43
In-life symptoms and signs	*n*	*n*(+ve) (%)	
Dyspnoea (marked)	722	180 24.9	
Rhonchi	715	326 45.6	
Sputum	723	438 60.5	
Cough	722	467 64.7	

[a] 21 Subjects were found not to have acceptable lung function after they were selected into the study
[b] All subjects had undergone lung function tests within 5 years of death except for one subject whose tests were within 7 years of death

strongest association with pack-years (the adjusted odds ratios (ORs) were 1.0 for non smokers, 2.1 (1.1–3.9) for <20 pack-years, 3.3 (1.75–6.2) for 20+ pack-years), and also with CDE [for the increasing dust levels the ORs were 1.0, 1.4 (0.9–2.2), 1.5 (1.0–2.3), 1.3 (0.9–2.0)]. Table 2 shows that mean lung function values decreased significantly with increasing severity of symptoms and signs. Table 3 shows the in-life predictors of lung function selected into the regression model (at the $P = 0.15$ level); rhonchi was the most significant predictor followed by dyspnoea. Of the environmental factors, pack-years was selected into the model, but CDE was not (this was the case even if rhonchi and dyspnoea were not included in the model). When CDE was kept in the model, the estimated regression coefficient was in fact positive, indicating a slight, positive trend between lung function and CDE. The model explained 37% of variability in FEV_1%, 31% variability in FVC% and 30% in FEV_1/FVC%.

Association between autopsy findings, lung function and clinical findings

Table 4 shows the multiple comparisons of baseline autopsy categories with higher categories, for lung function, and the test for trend for the clinical findings. Emphysema score was associated with increasing airflow impairment (FEV_1% predicted and FEV_1/FVC %), and with dyspnoea. Bronchitis was associated with some airflow impairment mainly in the moderate/marked category and with increased frequency of rhonchi, sputum and cough. A moderate/marked degree of bronchiolitis was associated with slightly reduced airflow and with increased frequency of sputum. There were only few subjects with marked bronchitis and bronchiolitis, and these were combined with the moderate categories. The degree of silicosis at autopsy was not associated with any of the COAD outcomes at autopsy (not shown). Figure 1 shows that there is a continuous exponential trend between FEV_1% predicted and the emphysema score. Indicated are the compensation categories for FEV_1% predicted.

To determine whether bronchitis in the absence of emphysema is associated with significant lung function impairment, we selected subjects with low emphysema score 0–5 ($n = 91$), and tested for trend between bronchitis and lung function. The mean FEV_1% (SD) decreased with the bronchitis scores, none, insignificant, and moderate/marked, as follows: 88.8% (22.4), 82.4% (13.5), $P = 0.19$, and 75.2% (17.4), $P = 0.01$, respectively. (P values are for multiple comparison of the means using the lowest category as a baseline.) The FEV_1/FVC% (SD) also decreased: 97.3% (8.3), 97.7% (8.5), $P = 0.89$, and 90.0% (11.6), $P = 0.001$. The data indicate that in the absence of emphysema, a moderate/marked degree of bronchitis is associated with mild lung function impairment only.

Of the risk factors tested for an association with emphysema, bronchitis and bronchiolitis (smoking pack-years, age, silicosis, and CDE), only smoking was associated significantly with all the autopsy outcomes (results not shown). The in-life COAD outcomes associated with these autopsy outcomes are shown in Table 4.

Table 2 Trends in mean lung function measurements with increasing severity of respiratory symptoms and signs (*FEV$_1$* one second forced expiratory volume, *FVC* forced vital capacity)

Lung function measure	Dyspnoea			Rhonchi			Sputum			Cough		
	None (n = 112)	Some (n = 414)	Marked (n = 175)	None (n = 376)	Some (n = 280)	Marked (n = 38)	None (n = 275)	Some (n = 414)	Marked (n = 13)	None (n = 247)	Some (n = 430)	Marked (n = 24)
FEV_1 %	78.20	67.12	53.01***	73.23	57.14	44.16***	70.85	62.18	51.39***	70.41	63.04	54.00***
Mean (SD)	(18.82)	(20.85)	(22.35)	(19.86)	(21.19)	(20.24)	(22.09)	(22.00)	(17.84)	(22.13)	(22.13)	(19.49)
FVC %	90.14	84.86	75.61***	87.47	79.30	72.37***	86.77	81.25	79.54***	86.39	81.80	80.25***
Mean (SD)	(15.81)	(15.61)	(16.84)	(15.97)	(16.25)	(15.62)	(16.56)	(16.38)	(16.68)	(17.07)	(16.17)	(17.43)
FEV_1/ FVC %	86.57	78.65	68.46***	83.43	71.13	59.50***	80.87	75.50	64.15***	80.70	76.03	66.71***
Mean (SD)	(14.21)	(19.11)	(20.92)	(17.29)	(19.49)	(19.48)	(18.63)	(20.16)	(17.35)	(18.62)	(20.10)	(18.78)

***$P < 0.001$

Table 3 Significant predictors of lung function obtained within 5 years of death (*FEV$_1$* one second forced expiratory volume, *FVC* forced vital capacity)

Predictor	FEV_1 (n = 692)			FVC (n = 692)			%FEV_1/FVC (n = 692)		
	Coefficient	SE	Partial r^2	Coefficient	SE	Partial r^2	Coefficient	SE	Partial r^2
Rhonchi	−0.4423	(0.0437)***	0.1531	−0.2630	(0.0451)***	0.0385	−8.5805	(0.8721)***	0.1336
Dyspnoea	−0.3138	(0.0414)***	0.0620	−0.2644	(0.0428)***	0.0802	−4.5080	(0.9259)***	0.0350
Height (cm)	0.0101	(0.0043)*	0.0049	0.0388	(0.0040)***	0.1356	−0.4365	(0.0872)***	0.0233
Weight (kg)	0.0114	(0.0019)***	0.0840	–	–	–	0.3801	(0.0379)***	0.0950
Age (years)	−0.0974	(0.0256)***	0.0444	−0.1027	(0.0266)***	0.0386	−0.1172	(0.0623)	0.0036
Age^2	0.0006	(0.0002)**	0.0098	0.0007	(0.0002)**	0.0113	–	–	–
Pack-years smoked	−0.0042	(0.0012)***	0.0118	−0.0031	(0.0013)*	0.0062	−0.0596	(0.0242)*	0.0083
Model r^2 (P value)	0.3700	(P = 0.0001)***	0.3700	0.3104	(P = 0.0001)***	0.3104	0.2989	(P = 0.0001)***	0.2989

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

– A variable was not selected into the model at 0.15 probability level

Table 4 Relationship of autopsy findings to lung function (mean values) and in-life symptoms and signs (percentage) (*FEV_1* one second forced expiratory volume, *FVC* forced vital capacity)

Autopsy findings	Lung function tests[a]			Clinical findings			
	FEV_1 (% predicted) Mean (S.D)	FVC (% predicted) Mean (S.D)	% FEV_1/FVC (% predicted) Mean (S.D)	Dyspnoea marked (n = 180) n (%)	Rhonchi any (n = 326) n (%)	Sputum any (n = 438) n (%)	Cough any (n = 467) n (%)
Emphysema score							
0–5 (n = 179)	78.8 (18.2)	84.7 (14.2)	92.7 (13.1)	25 (14.0)	61 (34.7)	103 (57.5)	113 (63.1)
5–35 (n = 329)	66.2 (21.6)***	84.8 (18.0)	77.2 (17.6)***	78 (23.7)	162 (50.0)	191 (58.5)	203 (61.9)
35–65 (n = 170)	52.0 (19.4)***	80.1 (16.5)*	63.9 (17.4)***	65 (38.2)	89 (52.4)	116 (68.2)	121 (71.2)
>65 (n = 18)	46.0 (18.7)	77.2 (15.1)	59.1 (21.5)***	9 (52.9)***	4 (23.5)*	13 (76.5)*	13 (76.5)
Bronchitis							
None (n = 126)	70.6 (22.7)	84.2 (15.3)	82.6 (18.5)	23 (18.3)	43 (34.4)	62 (49.2)	67 (53.2)
Insignificant (n = 350)	66.3 (21.9)	83.7 (16.8)	78.3 (19.7)*	88 (25.1)	150 (43.2)	209 (59.7)	224 (64.2)
Mod/marked (n = 248)	61.4 (22.4)**	82.5 (17.1)	73.4 (19.8)**	69 (28.1)*	1333 (54.7)***	167 (67.6)***	176 (71.3)***
Bronchiolitis							
None (n = 70)	66.6 (19.1)	84.1 (13.6)	78.9 (17.7)	18 (25.7)	35 (50.7)	35 (50.0)	42 (60.0)
Insignificant (n = 363)	67.1 (21.7)	84.1 (16.1)	79.0 (19.3)	90 (24.9)	148 (41.5)	217 (59.9)	231 (63.8)
Mod/marked (n = 291)	62.8 (23.8)*	82.3 (17.9)	75.0 (20.6)*	72 (24.7)	143 (49.5)	186 (63.9)*	194 (66.9)

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

[a] A multiple comparison test in analysis of variance was done using the lowest autopsy category as a comparison group, and a chi-squared test for trend was used

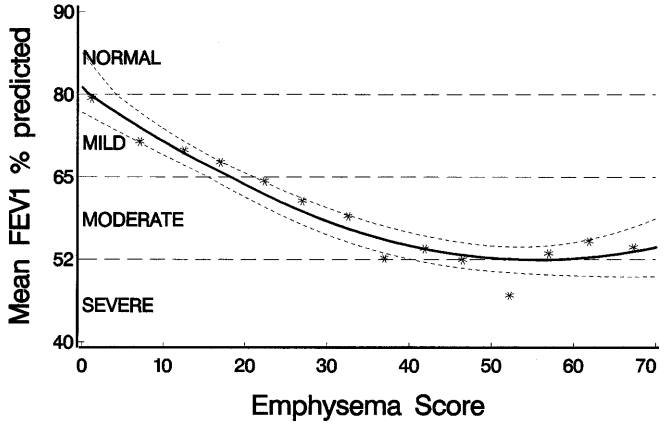

Fig. 1 Mean FEV_1 (%predicted) by emphysema score. In-life compensation impairment categories (normal, mild, moderate, severe) are indicated

Of the 706 subjects who had worked in dusty conditions, 306 had no silicosis, 202 had insignificant, 105 slight, 69 moderate and 24 marked degrees of silicosis at autopsy. The degree of silicosis was associated with increasing age at death and with CDE. The adjusted ORs (95% CI) for silicosis and increasing quartiles of years of age (<57, 57–62, 62–67, >67 years) were 1.0, 1.7 (1.01–2.9), 1.8 (1.1–3.2), 3.3 (1.9–5.7), respectively. The adjusted ORs (95% CI) for silicosis and increasing quartiles of CDE were 1.0, 4.5 (2.2–9.2), 7.2 (3.6–14.5), 17.6 (8.9–35.0). The strong association between silicosis and CDE indicates that the latter variable is reasonably reliable. However, the categories of silicosis (none, insignificant, slight, moderate and marked) were associated with decreasing emphysema score and decreasing tobacco pack-years. The age, height and smoking adjusted average emphysema scores were 22.9 (SE 1.2), 22.3 (SE 1.3), 23.3 (SE 1.9), 20.0 (SE 2.3), and 15.1 (SE 4.0), respectively. There was also an inverse association between smoking and CDE.

Table 5 shows whether the autopsy findings for COAD and silicosis are "predictive" of in-life lung function. Emphysema score and bronchitis were associated with decreased airflow (FEV_1 and FEV_1/FVC) and increased TLC. In the regression model for FEV_1, emphysema accounted for 65.4% of the variation explained by the model, height for 21.7%, age for 21.8%, bronchitis for 7%, and marked silicosis for 0.007%. Insignificant and slight silicosis at autopsy was not associated with decreased lung function. Despite the fact that silicosis was associated with decreasing emphysema score, moderate and marked silicosis showed decline in airflow, specifically in FEV_1 and $FEF_{25-75\%}$, and in TLC that was, however, not statistically significant.

Discussion

In South Africa, according to the Occupational Diseases in Mines and Works Act of 1973 and 1993, compensation award for COAD is based on lung function impairment in life, and on autopsy findings for emphysema, bronchitis, and bronchiolitis. The objective

Table 5 Autopsy-diagnosed findings as predictors of age- and height-adjusted lung function (*FEV_1* one second forced expiratory volume, *FVC* forced vital capacity, *$FEF_{25–75\%}$* forced mid-expiratory flow)

Predictor	FEV_1 Coefficient (SE)	FVC Coefficient (SE)	$\%FEV_1/FVC$ Coefficient (SE)	$FEF_{25–75\%}$ Coefficient (SE)	Total lung capacity Coefficient (SE)
Emphysema	−0.017 (0.001)***	−0.003 (0.001)*	−0.430 (0.026)***	−0.027 (0.002)***	0.022 (0.002)***
Bronchitis	−0.126 (0.041)**	−0.030 (0.044)	−2.800 (0.759)	−0.224 (0.058)***	0.139 (0.066)*
Bronchiolitis	−0.056 (0.046)	−0.050 (0.048)	−1.158 (0.839)	−0.040 (0.064)	−0.029 (0.074)
Silicosis 1 & 2[a]	0.056 (0.059)	0.035 (0.062)	1.289 (1.082)	0.045 (0.083)	−0.040 (0.094)
Silicosis 3[b]	−0.031 (0.096)	0.084 (0.100)	−1.966 (1.748)	−0.217 (0.133)	−0.332 (0.154)*
Silicosis 4[c]	−0.111 (0.157)	−0.160 (0.165)	−0.482 (2.863)	−0.228 (0.219)	−0.030 (0.237)
Model r^2	0.28***	0.20***	0.33***	0.29***	0.38***

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$
[a] Insignificant and slight silicosis
[b] Moderate
[c] Marked

of the study was to evaluate whether autopsy findings of COAD correlated with lung function impairment and respiratory symptoms and signs observed within 5 years prior to death, and the contribution of the individual autopsy findings to the lung function impairment.

We first assessed the reliability of the lung function and respiratory symptoms in life, by examining the associations between the in-life COAD outcomes and known risk factors for COAD (smoking, silica dust, age), and the associations among the in-life COAD outcomes. Smoking was significantly associated with respiratory symptoms, signs and lung function impairment, and all respiratory symptoms and signs were associated with decreasing lung function (see Table 2). However, in the multivariate analysis, only rhonchi and dyspnoea, but not cough and sputum, were selected as predictors (Table 3).

Next we related the in-life COAD outcomes to autopsy findings. Emphysema score categories 0–5, 5–35, 35–65, and >65 that are used for compensation purposes were associated with the average $FEV_1\%$ predicted of 78.8%, 66.2%, 52.0%, and 46.0%, respectively (see Table 4). These values of $FEV_1\%$ predicted are comparable to the lower limit of the $FEV_1\%$ ranges used for in-life compensation, viz. normal (≥80%), mild (79–65%), moderate (65–52%) and severe (< 52%) impairment. A continuous exponential relationship between $FEV_1\%$ predicted, and emphysema was observed (see Fig. 1). The subjects with the least amount of emphysema identifiable at autopsy already had measurable lung function impairment. The categories of impairment used for compensation are also indicated in Fig. 1. This figure indicates that in-life disability criteria and autopsy criteria based on emphysema are comparable. The figure can provide some guidelines for the evaluation of the current autopsy-based compensation criteria. Emphysema was most strongly associated with dyspnoea (see Table 4). Of the autopsy COAD outcomes, emphysema was also the most important predictor of lung function (Table 5), and accounted for 65.4% of the variation in FEV_1. However, the age and smoking adjusted emphysema score decreased with increased categories of silicosis and CDE.

Bronchitis at autopsy was also associated with impairment in $FEV_1\%$ predicted (see Table 4) and with increased frequency of rhonchi, sputum, and cough. However, in subjects without emphysema (score 0–5), even moderate/marked bronchitis was associated with mild airflow impairment only ($FEV_1\%$ predicted of 75%). For bronchiolitis, only moderate/marked degree was associated with airflow impairment ($FEV_1\%$ predicted of 62.8%) and with increased frequency of sputum. But when emphysema, bronchitis and bronchiolitis were related to lung function in a multivariate regression analysis, bronchiolitis was not statistically significant.

The association between lung function and silicosis at autopsy became apparent only after emphysema was adjusted for. This is because emphysema due to smoking was a predominant determinant of lung function in this group of miners (Table 5) and was inversely associated with silicosis. The association with silicosis was apparent for FEV_1 and $FEF_{25–75\%}$ (Table 5). Moderate silicosis was associated with some decrease in TLC, but marked silicosis was not. The results suggested that silicosis caused some obstructive as well as restrictive impairment in these miners. Whether it is silicosis per se, or the effect of silica dust on emphysema which is responsible for the obstructive lung function impairment, is often questioned. This study would support that silicosis per se, or small airways disease associated with silicosis, or airways thickening caused by silica dust, are associated with lung function loss, rather than is emphysema associated with silicosis.

Of the potential risk factors for COAD, only smoking was significantly associated with the COAD outcomes. CDE was not associated with any of the COAD outcomes. This reflects the strong association between emphysema and smoking, and the inverse relationship between tobacco pack-years and silicosis and CDE. The inverse relationships may reflect healthy worker effect and also the selection into the investigation.

The limitation of the study was that subject selection was determined by the availability of autopsy results, the type of autopsy findings for COAD, and the availability of lung function test results 5 years prior to death. Approximately 85% of white miners have an autopsy at death, but only those from whom whole-lung sections

had been taken, and with adequately preserved tissue to enable assessment of bronchitis and bronchiolitis, were selected. Of these, we chose all miners with autopsy findings of emphysema, bronchitis and bronchiolitis, and only a sample of miners without any, or minimal, COAD findings. There is no obvious reason why the quality of lung sections would be related to exposure. It is possible, however, that by over-sampling subjects with emphysema, bronchitis and bronchiolitis, we allowed heavy smokers with respiratory problems to be over-represented in the study. Availability of lung function tests 5 years prior to death was another selection issue. At the time when the study subjects had undergone lung function tests, such tests were done mainly on men requesting compensation, or presenting with medical problems. Thus, our investigation probably includes relatively healthy miners trying to get compensation or a higher degree of compensation, and miners with respiratory problems seeking medical examination or compensation.

Because of the complex selection process, we did not have a representative sample of miners. This is likely to have affected the association between the COAD outcomes and CDE, as previous studies have demonstrated these associations (see below). The above limitations are, however, unlikely to bias the association between autopsy findings and clinical findings for COAD.

The precise nature of the pathogenesis of chronic obstructive lung disease due to inhalation of silica dust is complex and not understood completely. According to the ATS standards (ATS 1987), emphysema is the most important pathological determinant of lung function impairment, and tobacco smoking is the main risk factor in the aetiology of emphysema. The results of our study support this. The association between emphysema and silica dust has been investigated in several autopsy-based studies. Becklake et al. (1987) has reported that South African gold miners with 20 years of working in a high dust environment, have a 12.7 (95% CI 3–52) times higher risk of having moderate emphysema in comparison with miners who never worked in high dust levels. No association between emphysema and silicosis was found. When the data from the study of Becklake et al. (1987) were adjusted for a selection bias, the OR decreased to 3.06 (95% CI 1.14–8.23) (de Beer et al. 1992). This revised result is more in line with a second autopsy study on South African gold miners, that found that those with the highest dust exposure had an OR of 1.6 (95% CI 0.8–2.0) for developing moderate/marked emphysema and, in addition, miners with moderate silicosis had a risk of emphysema of 2.0 (95% CI 1.2–3.5) (Hnizdo et al. 1991). According to the latter study, miners with both high dust exposure and silicosis had 3.2 times higher odds of developing moderate emphysema than those with low dust exposure and no silicosis. The effect of dust relative to the effect of smoking was, however, much smaller (Hnizdo et al. 1991). The smoking of 20 or more cigarettes per day increased the odds of developing moderate or marked emphysema by 28.3 times. A study of non-smoking gold miners found little emphysema, and that was not associated with dust or with functional impairment; silicosis showed, however, slight association with emphysema (Hnizdo et al. 1994). The autopsy-based investigations suggest that silica dust on its own probably causes only slight emphysema. Studies of lung function and deaths from COAD suggest that smoking can potentiate the effect of silica dust on COAD (Hnizdo 1992).

The association between emphysema and silicosis, observed in some reports might be due to silicosis acting as a surrogate variable for the effect of silica dust on emphysema. For example, in studies which used computer tomography, silicosis appeared to be associated with obstructive functional impairment but, after emphysema was adjusted for, the association disappeared and only emphysema remained correlated with impairment (Cowie et al. 1993; Bergin et al. 1986; Kinsella et al. 1990). Also, in a case control study of silicosis and COAD, silicosis was associated with obstructive impairment, but when CDE was adjusted for, the association between silicosis and lung function disappeared and only dust exposure was a significant predictor of lung function (Irwig and Rocks 1978). However, silicotic subjects were found to have impairment in $FEF_{25–75\%}$ (Irwig and Rocks 1978). In the study of Wiles et al. (1992), in which silicotic and non-silicotic gold miners were matched for smoking and dust exposure, in all of the comprehensive tests done, only the slope of the alveolar plateau (phase 3) and the closing volume were significantly higher in silicotic subjects; this applied even for those with marked degrees of silicosis. These two studies, as well as a study of silica dust exposed Chinese workers (Chia et al. 1992), suggest an association between silicosis and small airways disease, rather than an association between silicosis and emphysema. Results from our work show that when emphysema and bronchitis (mainly due to smoking) were adjusted for, moderate and marked silicosis showed a decline in airflow parameters, FEV_1 and $FEF_{25–75\%}$, and in TLC. These results suggest the presence of some obstructive and restrictive impairment independent of emphysema.

Experimental and case studies have demonstrated the existence of a small airway lesion specific to mineral dust, namely mineral dust airway disease (MDAD) (Churg et al. 1985, 1989), which is reported to be morphologically distinguishable from small airway disease caused by tobacco smoke, and consists mainly of marked fibrosis and pigmentation of the respiratory bronchioles. Patients with MDAD can have significant abnormalities of FEV_1, $FEF_{25–75}$, vital capacity (VC) and nitrogen washout (Churg et al. 1985). Lesions in the small airways can be reliably detected by tests of closing capacity and the slope of alveolar phase III of the single breath washout curve even when other tests are normal (Cosio et al. 1978).

Epidemiologic studies done on black South African miners reported, however, that silicosis is associated with a substantial lung function loss (Cowie and Mabena 1991; Steen et al. 1997; Cowie 1998; Trapido et al.

1998). Men with category 3/3 silicosis, compared with those without silicosis, had a reduction of FEV_1 of 447 ml after the effect of tobacco smoking and duration of dust exposure were controlled for (Cowie and Mabena 1991). The differences between the two groups of miners may be due to more severe silicosis in black miners. However, age-adjusted autopsy data collected from 1974 to 1990 on some 70,000 miners, did not show that black miners had a substantially higher prevalence or severity of silicosis than white miners. However, the former do have a much higher incidence of pulmonary tuberculosis which increases substantially with the severity of silicosis (Cowie 1994; Murray et al. 1996) and with increasing dust exposure (Kleinschmidt and Churchyard 1997). A significant association between a past history of tuberculosis and loss of lung function has been observed in a study of former gold miners from Botswana (Steen et al. 1997). Further, the losses of lung function were observed to increase with the number of treated pulmonary tuberculosis episodes; the residual loss of FEV_1 was 153 ml after one episode, 326 ml after two, and 410 ml after three episodes, the corresponding losses for FVC being 96 ml, 286 ml, and 345 ml (Hnizdo et al. 1999). Thus the effect of silica dust and silicosis on lung function in black miners is worse due to complications with associated tuberculosis.

In conclusion, we found that the data from the present study show that pathological assessment of emphysema, as done at NCOH for compensation purposes, correlates strongly with the results of lung function tests for airflow obstruction. Moreover, compensation based on autopsy findings for emphysema appears to be comparable with that based on in-life lung function impairment. Emphysema was the best predictor of lung function loss in life. Although there is some association between lung function loss and bronchitis and bronchiolitis at autopsy, the degree of impairment remained statistically insignificant after emphysema was taken into account. The loss of lung function associated with simple moderate and marked silicosis as seen in the studied miners was suggestive of an obstructive and restrictive type. The lack of association between emphysema and dust exposure is a likely reflection of the process by which miners were selected for this study.

The study has been approved by the Committee for Research on Human Subjects of the University of the Witwatersrand, Johannesburg, South Africa.

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