UNIVERSITY OF CAPE TOWN

AN EVALUATION OF MORTALITY RATES AND THEIR DETERMINANTS IN A SOUTH AFRICAN COHORT OF FORMER ASBESTOS MINERS

by

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A research report submitted to the School of Public Health, Faculty of Health Sciences, at the University of Cape Town in partial fulfilment of the requirement for the award of the degree of Master of Medicine (MMed) in Occupational Medicine

-February 2025-

DECLARATION

AN EVALUATION OF MORTALITY RATES AND THEIR DETERMINANTS IN A SOUTH AFRICAN COHORT OF FORMER ASBESTOS MINERS

I, **Yumna Williams-Mohamed,** hereby submit my dissertation for the degree of Master of Medicine (MMed) in Occupational Medicine. I declare that this is my original work and any references to the work of others have been appropriately cited and acknowledged. I further declare that neither the whole work, nor any part of it, has been, is being, or is to be submitted for another degree at this or any other university. This work has not been reported or published prior to registration for the above-mentioned degree.

I declare that this dissertation has been submitted to the Turnitin module (or an equivalent similarity and originality checking software) as required for the completion of my degree. I confirm that my Turnitin report has been reviewed by my supervisor, and any concerns identified regarding similarity or potential plagiarism have been resolved through consultation.

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DEDICATION

This dissertation is dedicated:

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Abbreviations and Acronyms

aHR	Adjusted Hazard Ratio
ARD	Asbestos-related Disease
ATS	American Thoracic Society
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
CMR	Crude Mortality Rate
ERS	European Respiratory Society
FEV_1/FVC ratio	Forced Expiratory Volume/Forced Vital Capacity Ratio
FEV_1	Forced Expiratory Volume exhaled in 1 second
Fibre/ml-year	Fibres per millilitre year
FVC	Forced Vital Capacity
GLI	Global Lung Function Initiative
IARC	International Agency for Research on Cancer
ILO	International Labour Organization
Inyosi	Electronic database of the Asbestos and Kgalagadi Relief Trusts
SMR	Standardised Mortality Ratio
SOMP	Specialist Occupational Medicine Panel
SRR	Standardised Rate Ratio
TB	Tuberculosis
Trusts	Asbestos Relief and Kgalagadi Relief Trusts
XDS	Xpert Decision Systems

ABSTRACT

AN EVALUATION OF MORTALITY RATES AND THEIR DETERMINANTS IN A COHORT OF FORMER ASBESTOS MINERS IN SOUTH AFRICA

Background: There is a well-established causal link between occupational asbestos exposure and lung diseases such as pneumoconiosis and mesothelioma. Higher mortality rates in former asbestos miners compared to the general population are thus anticipated. However, no local, large-scale studies have been conducted to evaluate the all-cause mortality experience in this subpopulation. We investigated all-cause mortality among a cohort of former South African asbestos miners captured on the Asbestos and Kgalagadi Relief Trusts' Inyosi database.

Methods: All-cause standard mortality ratios (SMRs) and crude mortality rates (CMRs) were calculated for 11 343 ex-miners. Mortality predictors were modelled using Cox regression analysis and mortality trends were assessed by examining annual all-cause CMRs and SMRs over the 20-year study period.

Results: The cohort's all-cause mortality exceeded that of the general population by 4% (SMR=1.04; 95% CI: 1.01-1.07). Radiological abnormalities based on ILO profusion category were strong predictors of mortality with adjusted hazard ratios (aHRs) ranging from 1.13 (95% CI: 1.05-1.23) to 2.34 (95% CI: 1.52-3.58). Other significant predictors were a BMI less than 18.5 kg/m^2 (aHR=1.46; 95% CI: 1.35-1.58), history of previous smoking (aHR=1.43; 95% CI: 1.35-1.53), costophrenic angle obliteration (aHR=1.27; 95% CI: 1.14-1.41), and reduced forced expiratory volume in one second and forced vital capacity (aHR=1.60; 95% CI:1.41-1.81 and aHR=1.26: 95% CI: 1.12-1.42, respectively, for z-scores less than -3.0). The SMR decreased with time.

Conclusion: Interpretation of mortality in this cohort was limited by incomplete data, preventing firm conclusions. However, radiologic and spirometric measures emerged as significant predictors of mortality, potentially enabling risk stratification and guiding targeted interventions. Such interventions include early management of respiratory complications and smoking cessation, which could mitigate mortality risk.

Keywords: asbestos-related disease, mortality rates, asbestos miners, predictors, risk factors, determinants

SECTION II: JOURNAL MANUSCRIPT

AN EVALUATION OF MORTALITY RATES AND THEIR DETERMINANTS IN A SOUTH AFRICAN COHORT OF FORMER ASBESTOS MINERS

This manuscript has been prepared to be submitted for publication in the American Journal of Industrial Medicine. The format of the article follows the journal's guidelines for authors (**Appendix 8**).

AMERICAN JOURNAL OF INDUSTRIAL MEDICINE: TITLE PAGE

AN EVALUATION OF MORTALITY RATES AND THEIR DETERMINANTS IN A SOUTH AFRICAN COHORT OF FORMER ASBESTOS MINERS

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Shahieda Adams: Assisted with the design of the study, assisted with data interpretation and revised the study critically for intellectual content.

Rodney Ehrlich: Conceived the study, assisted with data interpretation and revised the study critically for important intellectual content.

Jim teWaterNaude: Assisted with the acquisition of data and revising the study critically for intellectual content.

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Author Disclosure

The authors declare no conflicts of interest. Dr Jim teWaterNaude was employed at the Asbestos Relief Trust between 2005 and 2013 as a consultant and as their medical co-ordinator from 2005 onwards.

Disclaimer

None

ABSTRACT

AN EVALUATION OF MORTALITY RATES AND THEIR DETERMINANTS IN A COHORT OF FORMER ASBESTOS MINERS IN SOUTH AFRICA

Background: There is a well-established causal link between occupational asbestos exposure and lung diseases such as pneumoconiosis and mesothelioma. Higher mortality rates in former asbestos miners compared to the general population are thus anticipated. However, no local, large-scale studies have been conducted to evaluate the all-cause mortality experience in this subpopulation. We investigated all-cause mortality among a cohort of former South African asbestos miners captured on the Asbestos and Kgalagadi Relief Trusts' Inyosi database.

Methods: All-cause standard mortality ratios (SMRs) and crude mortality rates (CMRs) were calculated for 11 343 ex-miners. Mortality predictors were modelled using Cox regression analysis and mortality trends were assessed by examining annual all-cause CMRs and SMRs over the 20-year study period.

Results: The cohort's all-cause mortality exceeded that of the general population by 4% (SMR=1.04; 95% CI: 1.01-1.07). Radiological abnormalities based on ILO profusion category were strong predictors of mortality with adjusted hazard ratios (aHRs) ranging from 1.13 (95% CI: 1.05-1.23) to 2.34 (95% CI: 1.52-3.58). Other significant predictors were a BMI less than 18.5 kg/m^2 (aHR=1.46; 95% CI: 1.35-1.58), history of previous smoking (aHR=1.43; 95% CI: 1.35-1.53), costophrenic angle obliteration (aHR=1.27; 95% CI: 1.14-1.41), and reduced forced expiratory volume in one second and forced vital capacity (aHR=1.60; 95% CI: 1.41-1.81 and aHR=1.26: 95% CI: 1.12-1.42, respectively, for z-scores less than -3.0). The SMR decreased with time.

Conclusion: Interpretation of mortality in this cohort was limited by incomplete data, preventing firm conclusions. However, radiologic and spirometric measures emerged as significant predictors of mortality, potentially enabling risk stratification and guiding targeted interventions. Such interventions include early management of respiratory complications and smoking cessation, which could mitigate mortality risk.

Keywords: asbestos-related disease, mortality rates, asbestos miners, predictors, risk factors, determinants

1. INTRODUCTION

Historically, South Africa has contributed significantly to the global asbestos market, producing approximately 97% of crocidolite, 100% of amosite, and holding the position as the fifth-largest producer of chrysotile asbestos.[1] Peak production occurred in the late 1970s.[1] However, mounting scientific evidence has conclusively demonstrated the severe health risks associated with asbestos exposure, most notably its carcinogenic potential. This compelling evidence ultimately led to the official prohibition of new asbestos mining, production, and utilisation in South Africa on 28 March 2008.[2] This ban did not include pre-existing asbestos-containing materials such as those used in roof repair and replacement. Consequently, the potential for occupational and, moreover, environmental exposure to asbestos has persisted.[3]

The causal link between asbestos exposure and a range of pulmonary and non-pulmonary diseases including asbestosis, pleural disease, lung cancer, mesothelioma and cancers of the larynx and ovary is well established, while the evidence linking asbestos exposure to gastrointestinal cancers is less conclusive.[4-17] Higher morbidity and mortality rates are thus anticipated in former asbestos miners relative to the general population. Several international studies have documented higher all-cause and cause-specific standardised mortality ratios (SMRs) among asbestos-exposed workers, including miners.[4-17] Early studies by Musk et al (2008) reported a statistically significantly increased SMR for pneumoconiosis (SMR=15.5), lung cancer (SMR=1.52), respiratory diseases (SMR=1.58) and ill-defined diseases (SMR=2.00)[6]; while Wang et al (2013) reported a statistically significant increased SMR for all-cause mortality (SMR=1.46), parenchymal asbestosis (SMR=9.62), lung cancer (SMR=1.52) and pulmonary-related cardiac disease (SMR=2.70).[11] More recently, in an updated Italian cohort study examining mortality amongst chrysotile-exposed miners, Ferrante et al (2020) reported a significantly increased SMR for all-cause mortality (SMR=1.28; 95% CI: 1.17-1.40), parenchymal asbestosis (SMR=375.06; 95% CI: 262.68-519.23) and mesothelioma (SMR=4.30; 95% CI: 1.58-9.37).[4] Similarly, an Italian study by Pira et al (2017) reported an increased SMR for all-cause mortality (SMR=1.35; 95% CI: 1.25-1.45) and mesothelioma (SMR=5.54; 95% CI: 2.22-11.4) in asbestos-exposed miners.[5] In contrast, research from South Africa, a nation with a thriving asbestos mining industry throughout the 1970s, has produced limited data regarding the overall mortality pattern in exposed worker cohorts. The true burden of asbestos-related morbidity and mortality in this population thus remains largely unquantified.

Furthermore, local and international studies have consistently shown that asbestos-related disease (pulmonary and systemic) remains underdiagnosed, untreated and uncompensated.[18-20] This suggests that medical surveillance programmes and compensation systems may be suboptimal in capturing the true burden of asbestos-related disease. Ongoing medical surveillance in former asbestos miners remains pertinent given the long latency period for asbestos-related diseases and the lack of a clearly defined threshold for exposure intensity and duration. Studies have suggested that former asbestos miners endure chronic health and financial burdens, denying them any share in the wealth their labour generated.[20]

In recognition of the enduring health risks associated with mining exposures, South African legislation in the form of the Occupational Diseases and Mine Works Act (ODMWA) entitles former miners to a post-employment biennial benefit medical examination (BME) at an accredited medical facility or medical practice.[21] The BME is aimed at identifying compensable occupational lung disease in miners who have worked on South African mines and who have not reached maximum workers' compensation. ODMWA does not allow for ongoing medical surveillance once maximum compensation is reached. Those at future risk of developing mesothelioma, for example, will therefore not undergo further mandatory surveillance once maximum compensation has been reached. Notably, environmental exposure to asbestos resulting in disease is not addressed in the statute and therefore, not compensable.

The Asbestos Relief and Kgalagadi Relief Trusts (the "Trusts") were established in March 2003 and February 2006, respectively, to mitigate the financial and socioeconomic burden suffered by former asbestos miners. This followed litigation against asbestos mining companies by former asbestos-exposed miners and communities. The Trusts provide a comprehensive suite of services encompassing both financial recompense for qualifying asbestos-related disease and palliative care interventions. Funded by asbestos mining companies that previously operated in South Africa, the Trusts aimed to compensate claimants previously employed at qualifying mines for asbestos-related disease, based primarily on the severity of radiological and spirometry findings, and to improve the quality of life of affected individuals.[22] A comprehensive database with claimants' health assessment and compensation data was maintained by the Trusts, namely the Inyosi database. It was used primarily for administrative purposes, but also provided an opportunity to study the mortality experience of this large cohort of asbestos-exposed miners.

Most Trust claimants resided in the Northern Cape, Mpumalanga, and Limpopo provinces of South Africa, which were historically the centres of commercial crocidolite, chrysotile, and amosite asbestos mining, respectively.[23] Data released by the Trusts in 2006 indicated that most claimants (70,6%) were from the Northern Cape.[23] A 1995 survey provides valuable sociodemographic context to the areas where miners lived and worked, revealing persistent socioeconomic challenges in the Northern Cape, such as low education levels (only 21% of adults had completed secondary schooling) and high unemployment

(27%).[24] Socioeconomic disparities were particularly evident among Black households, where 38% had low annual incomes, only 27% had access to drinking water, and 85% relied on public healthcare facilities.[24] Post-1994, the Northern Cape showed no immediate, notable socio-economic advancement, despite demographic transition at the national level.[25]

This study, conducted on a cohort of former asbestos miners captured on the Asbestos Relief and Kgalagadi Trusts' database, has three aims: (a) to quantify the all-cause standardised mortality rate (SMR); (b) to identify the demographic, occupational and clinical predictors of mortality in this cohort; and (c) to outline mortality trends over the study period. The data generated has the potential to better quantify the mortality experience of this cohort, evaluate the burden of asbestos-related disease, provide motivation for the rational design of medical surveillance programmes and facilitate access to adequate compensation.

2. METHODS

Written informed consent was obtained from study participants on entering the Asbestos Relief and Kgalagadi Trusts' Inyosi database, which included consent to the use of the data for future research. This study was based on anonymised secondary data obtained from the Inyosi database and was approved by the academic institution's Human Research Ethics Committee (HREC Ref: 625/2024).

2.1. Study Design, Data Source and Study Population

A retrospective cohort mortality study was conducted on former asbestos miners captured as potential claimants on the Trusts' Inyosi database. The electronic database, estimated to represent potential claimants from approximately 85% of South African asbestos mines,[26] was primarily established for compensation purposes and spanned two decades from its inception in 2003 until present. The last asbestos mine in South Africa closed in 2002. Participant uptake of the Trusts' benefits and entry onto the database was higher in the earlier years of the study, particularly 2004 to 2009, with numbers declining significantly thereafter (Figure S1: Supplementary information). Individuals were eligible for the Trusts' benefits and admission onto the database based on a demonstrated history of occupational asbestos exposure while employed at a qualifying mining operation. Following admission, all participants had a baseline medical assessment including a physical examination, chest radiograph (CXR) and spirogram. The clinical data, mainly the radiological and spirometric findings, were used to categorise asbestos-related pulmonary disease in participants. This in turn, informed the eligibility for compensation. This study was conducted on 11 343 participants captured on the Inyosi database between 1 January 2004 and 21 March 2023.

2.2. Measurement Tools and Quality Control

2.2.1 The Asbestos and Kgalagadi Relief Trust Medical Evaluation Form

A standardised medical evaluation form (**Appendix 2**) was used by Trust-employed clinicians to record participant data. Demographic data included age and biological sex; the medical history included previous illnesses and comorbidities; and the occupational data included the type of exposure, duration of asbestos exposure, the nature of work performed and the mine location. Occupational data were verified using occupational records, where available.

2.2.2 The Specialist Occupational Medicine Panel Data Collection Form

A Specialist Occupational Medicine Panel (SOMP) panel was responsible for classifying asbestos-related disease (ARD) in participants using a composite system of clinical, radiological, spirometric and histological findings. Diagnostic criteria for ARD categories 1-4 are outlined in **Table I**. SOMP members, primarily radiologists and experienced occupational medicine clinicians trained in the International Labour Organization's (ILO) Classification of Radiographs of Pneumoconioses,[27] utilised a standardised form (**Appendix 3**) to summarise clinical examination findings and document radiological and spirometry data for each participant.

CXRs were interpreted in accordance with the ILO Classification and with the knowledge of the participant's medical, occupational, and cigarette-smoking history. Radiological classification was established through consensus between the radiologist and occupational medicine clinician at a joint sitting, with the radiologist's interpretation prioritised. Where classification was borderline, or where panellists were unsure of the presence of asbestosis, a different SOMP panel was enlisted to classify the CXR. In such cases, the report of the SOMP panel making the higher classification was used. Where a difference of opinion persisted, a specially convened six-member SOMP panel reviewed the CXR to make a final determination.

Spirometry was conducted on participants in accordance with current European Thoracic Society/ American Thoracic Society (ERS/ATS) guidelines.[28,29] Lung function abnormalities identified in participants were classified based on spirometry reference values established by the European Community of Coal and Steel (ECSC), without correcting for race.[30] Each participant was then assigned an asbestos-related (ARD) classification based on radiological and spirometry data, which served as the basis for determining eligibility for compensation. In cases where parenchymal asbestosis or pleural disease coexisted with malignancy, the more severe asbestos-related disease, i.e. malignancy, determined the ARD grade. Grading was guided by specific criteria utilised by the Trusts, as outlined in **Table I**. The quality of CXRs and spirograms was assessed prior to reading and interpretation (Table SI: Supplementary information).

This study utilised Global Lung Function Initiative (GLI) reference equations to generate standardised FEV_1-, FVC- and the FEV_1/FVC ratio z-scores for each participant. Raw FEV_1 and FVC values captured on the SOMP forms, in conjunction with individual participant data (age, sex, height) and the GLI "other ethnic category", were used for the calculation.[31] An online ERS GLI calculator facilitated these calculations.[32] A z-score threshold of -1.64 was applied to dichotomise raw FEV_1 and FVC values into normal and low categories. Low FEV_1- and FVC z-scores were subcategorised further using GLI z-scores as outlined in **Table I**. FEV_1 and FVC z-scores were independently evaluated as risk factors for mortality. Table I provides a concise overview of key variables, encompassing ILO profusion and spirometry classification, in addition to quality control measures implemented to ensure data integrity. A more comprehensive presentation of these details is available in the supplementary information (Table SI: Supplementary information).

2.3 Vital Status Assessment and Sample Size

The data of all individuals captured on the Inyosi database during the study period were analysed, following the application of exclusion criteria. Vital status data, including the date of death of deceased cohort participants, were obtained by the Trust for operational purposes on 21 March 2023 through a linkage process facilitated by Xpert Decision Systems (XDS). XDS is an independent third-party linkage specialist able to access the South African Department of Home Affairs (DHA) database and provide vital status data for a given South African identity (ID) number. The South African ID numbers of all 16 127 claimants on the Inyosi database were submitted via XDS to the DHA on 21 March 2023. Due to the historical inaccuracy of cause-of-death recording and the cost implications of such a search, cause-of-death information was not requested.[33] Following the removal of non-occupationally exposed participants and those with invalid or non-matching ID numbers, an anonymised record of the linked database consisting of 12 344 participants was obtained from the Trusts. The study sample was further reduced following the removal of participants who died before the commencement of the defined study period (n=124) and duplicate entries (n=877). A total of 11 343 study participants were included in the final analysis, with full spirometry data for analysis and interpretation available for 10 563 participants.

3. STATISTICAL ANALYSIS

All statistical analyses were performed using STATA version 18.0.[34] Descriptive statistics were used to summarise the distribution of predictor variables across vital status groups (deceased or alive). Ninety-five percent confidence intervals (CIs) were calculated, and statistically significant differences in the distribution of categorical variables, by vital status, were assessed using Chi-squared tests and were reported using p-values.

A comparative analysis of mortality ratios between the study population and the general South African population was conducted using SMRs. The SMRs were computed by dividing the observed number of deaths by the number of deaths expected in the general South African population matched for age, sex, and calendar year. Racial ascription was not recorded on the database and was thus excluded from the standardisation calculation. Actuaries calculated the expected mortality for the general South African population using the Thembisa Model Version 4.7 with COVID-19 pandemic adjustments based on data from the South African Medical Research Council.[35,36]

Additional mortality measures described in this study include annual crude mortality rates (CMRs) and adjusted hazard ratios. To provide an overview of mortality risks in the study population, CMRs were calculated by dividing the number of observed deaths by the person-years contributed overall and for each year in the time series or stratum of the predictor of interest i.e., CMRs were calculated as incidence densities.

A Cox Proportional Regression Model was employed to identify demographic, occupational, and clinical predictors of mortality while adjusting for all covariates. Survival time was calculated as the total number of days (converted to years) from the date of entry into the study and either the date of death or the censoring date (21 March 2023) for surviving participants. Adjusted Hazard Ratios (aHRs) with 95% confidence intervals were reported. The validity of the model and the proportionality assumption were assessed statistically and graphically using Schoenfeld residuals. Kaplan-Meier plots were used to illustrate graphically the differences in survival probability between study participants with and without low FEV_1- or FVC z-scores. A log-rank test was used to assess if differences between the strata were significant. While CMRs and cumulative incidences provide a general understanding of the overall burden of mortality, more robust adjusted hazard ratios modelled in the Cox Regression identified predictors and time-sensitive changes in the mortality rates of the study population while adjusting for covariates.

Mortality trends were established by computing the CMR and SMR for each year of the study, which were used to elucidate temporal variations in mortality risk. A linear regression was modelled to determine the average change in crude mortality rates per annum.

To explore a synergistic effect between cigarette smoking and asbestos exposure on the hazard of mortality, an interaction term was modelled between smoking status and ILO profusion category. An increased hazard of mortality was observed in smokers with more severe radiological evidence of parenchymal asbestosis (ILO profusion categories 2 and 3) relative to non-smokers with no radiological evidence of parenchymal asbestosis. However, none reached statistical significance (Table SIII: Supplementary information). Small numbers in the strata suggest that the study may have lacked statistical power to detect significant differences.

4. RESULTS

4.1 Demographic, Occupational and Clinical Characteristics and Crude Mortality Rates

The characteristics of the 11 343 study participants stratified by vital status are presented in **Table II**, along with crude mortality rates. The median age at entry onto the cohort was 53.1 years (IQR: 47.01; 61.97), most participants were male (82.8%) and non-smokers (68.4%). The type of asbestos exposure was unspecified in 33.1% of participants. Crocidolite exposure was most prevalent (43.1%), with 20.6% of participants exposed to chrysotile asbestos and 2.5% exposed to amosite asbestos. Most workers were employed aboveground only (75.8%). The majority also had less than five years of exposure duration (67.4%), with only 0.7% exposed for a period exceeding 15 years. While 20.8% had radiographic opacities characteristic of asbestosis, only 1.7% of the overall group were classified into more severe ILO profusion categories 2 and 3. An abnormal ("low") FEV_1 z-score was present in 37.0% and FVC z-score in 37.8% of the cohort, respectively. Furthermore, 63.1% of participants did not meet the Trust criteria for ARD, while 29.0% presented with ARD 1. ARD categories 2 to 4 exhibited significantly lower prevalence, with observed rates of 3.3% for ARD 2, 0.4% for ARD 3, and 2.3% for ARD 4. The quality assessment of radiological data indicated that approximately 92.1% of CXRs were readable, with 7.5% not having a quality classification documented. Similarly, 86.7% of spirograms were interpretable, with 12.6% not having a quality classification documented.

During the 20-year follow-up period, a total of 136 548.92 person-years had been accrued and 45.0% (n=5 106) of the cohort had died, resulting in an overall CMR of 37.4 per 1 000 person-years. Notably, a significant proportion of deaths (43.7%) occurred before the age of 55 years.

Excluding an outlier of 69.1 per 1000 person-years in 2021 (coinciding with the COVID-19 pandemic), on visual inspection, CMRs exhibited a slight upward trend between 2004 and 2023 (Table SII and Figure S2: Supplementary information). With the same exclusion, linear regression analysis revealed an average annual increase in the CMR of 0.6 per 1000 person-years (Figure S3: Supplementary information).

4.2 Demographic, Occupational and Clinical Predictors of Mortality

Cox regression analysis identified several predictors of mortality (**Table III**). Demographic factors associated with an increased hazard of death included age, male sex, and a history of cigarette smoking. Among occupational factors, exclusive aboveground employment was strongly associated with an increased hazard of death, as was underweight status among clinical factors.

Radiological predictors of mortality included ILO profusion category (overall aHR=1.43; 95% CI: 1.36; 1.51, p-trend= 0.000) and costophrenic angle obliteration. Relative to participants with normal lung function, impaired lung function, operationalised here as reduced FEV_1- or FVC z-scores, significantly and independently predicted mortality. Kaplan-Meier survival curves (**Figure 1**) graphically demonstrate the significant difference in survival probabilities in participants with and without a reduced FEV_1- or FVC z-score, confirmed by a significant log-rank test across strata in both categories (p=0.000). The relationship between reduced lung function and the hazard of mortality demonstrated a threshold effect at moderately low levels for FEV_1 z-scores and severely low levels for FVC z-scores. Below that, there was a questionable difference from normal. Notably, a reduced FEV_1 z-score emerged as a stronger prognostic indicator compared to a reduced FVC z-score.

As expected, a significant association was observed between ARD classification as per SOMP and the hazard of death. An elevated hazard of mortality was observed in participants with radiological evidence of either parenchymal asbestosis or asbestos-related pleural disease and impaired lung function relative to those with normal radiological and spirometry findings (aHR=1.14; 95%CI: 1.04-1.25 for ARD 1). Individuals with malignancy, specifically asbestos-related lung cancer (ARD 3) and mesothelioma (ARD 4), exhibited significantly elevated aHRs relative to those with no ARD (aHR=3.85; 95% CI: 2.47-6.01 for ARD 3 and aHR=6.35; 95% CI: 5.42-7.45 for ARD 4).

4.3 Model Diagnostics

Deviations from the proportional hazards assumption were observed for BMI (overweight and obese), diffuse pleural thickening, and FEV_1 z-score, with only the latter significantly predicting mortality. To account for these violations, an extended Cox model was employed, incorporating these covariates as time-varying variables (Table SIV: Supplementary information). While the hazard ratios for these time-varying covariates changed over time, the adjusted hazard ratios for the primary predictors remained consistent with those obtained from the original Cox model. This concordance suggested that the non-proportionality of the covariates did not influence the estimates of the primary associations significantly. Thus, the original Cox model remained valid for assessing the association between the primary predictors and the mortality outcome. Regarding the FEV_1 z-score, although it violated the proportional hazards assumption, its effect in the original model can still be interpreted, but with the caveat that its influence on the outcome may vary over time.

4.4 Standardised Mortality Ratios and Trends

Table IV presents SMRs for the study cohort relative to the general South African population by calendar year, adjusted for age and sex. Due to the absence of recorded racial data, racial stratification was not incorporated into the SMR calculation. The overall (all-year) mortality rate within the cohort was 4% higher than that of the general population (SMR=1.04; 95% CI: 1.01-1.07). A significantly elevated mortality rate was observed among females (SMR=1.17; 95% CI: 1.09-1.25) compared to equivalent strata in the general population. In contrast, no significant excess mortality was detected among males (SMR=1.02; 95% CI: 0.99-1.05).

Stratification by five-year age-groups revealed elevated SMRs in two non-adjacent strata: 50-54.9 years and 60-64.9 years. SMR by calendar year (**Table IV and Figure 2**) showed a rise from 0.85 in 2004 to a peak of 1.29 in 2010, followed by a slow decline to 1.09 in 2018. The period 2019-2023, which coincided with the COVID-19 pandemic, is characterised by sharp fluctuation. Barring a small spike (1.06) observed at the height of the pandemic in 2021, a steady decline in the SMR was observed with no excess mortality recorded from 2019 onwards.

5. DISCUSSION

In summary, this cohort study of former South African asbestos miners revealed a marginal overall excess in mortality compared to the general population. However, temporal analysis revealed a significant increase in mortality before the age of 55 years, and notable disparities between sexes. ILO profusion category and ARD grade emerged as the strongest predictors of mortality risk, while demographic and spirometric factors also demonstrated prognostic value. The large majority (> 90%) of participants presented with no detectable or mild parenchymal asbestosis (ILO profusion category 0 and 1), while 63.1% presented with no ARD as per SOMP classification (normal radiological and spirometry findings). As expected, those diagnosed with malignancy (ARD 3 and 4) had a strongly elevated mortality risk. Over the 20-year study period, SMRs initially rose, plateaued between 2011 and 2018, and subsequently declined.

Did the cohort demonstrate excess mortality (elevated SMR)?

An overall excess mortality of 4% within this cohort of asbestos miners was observed relative to the general South African population. This was notably lower than studies conducted on chrysotile-exposed miners in Italy (SMR=1.28) and China (SMR=1.46).[3,10] While factors such as the presence of comorbidities and differences in the intensity and duration of exposure could account for these differences, a potential explanation for this lower-than-expected excess mortality within this cohort lies in survivorship bias. Considering the peak of the asbestos industry in South Africa in the 1970s and the latency period of asbestos-related diseases, it is plausible that a portion of this cohort died prior to the establishment of the cohort in 2003 and the study's commencement in 2004. Individuals who survived longer without developing fatal asbestos-related diseases were more likely to be included in the study, potentially contributing to attenuation in the observed mortality. An evaluation of employment data is required to estimate the proportion of miners who might have died before cohort inception.

In addition, the relatively short employment duration experienced by a substantial proportion of miners within this study cohort (less than five years in 67.4% of the cohort) may have contributed to the attenuated mortality risk. The possibility exists that many workers with longer employment duration may have died before entry onto the database. Notably, employment duration data were unavailable in 23.6% of the cohort, which could have included miners with longer employment duration. Inaccurate employment records and broken service are potential factors that may have contributed to this finding.

Another factor to consider is the potential influence of the cohort's baseline health status. A healthier cohort with lower pre-existing morbidity might exhibit lower overall mortality rates, regardless of asbestos exposure. However, as comprehensive comorbidity data were not systematically collected for the study population, this hypothesis remains speculative. Finally, potential inconsistencies in mortality data reporting and categorisation within the database could have inadvertently underestimated mortality rates.

The denominator in the SMR calculation, i.e., expected mortality rate for the general South African population, warrants consideration when interpreting the SMRs in this mining cohort. Although adjustments for sex and age were made, critical factors such as socioeconomic status (SES), racial ascription, geographic location and the background prevalence of disease were not accounted for in the analysis. Higher expected background mortality rates would be anticipated in lower socioeconomic strata and in certain geographic locations associated with higher background prevalence of disease.[37] Dilution of the comparison population by the inclusion of higher SES strata could therefore result in overestimation of the SMR for this cohort. In addition, the absence of reliable provincial mortality data prevented its use as the reference population in the calculation of SMRs. While provincial data may also have contained some bias, it would likely have offered a more representative and context-specific comparison than national data, potentially resulting in more accurate SMR estimates.

This study demonstrated a significant mortality burden, with 43.7% of deaths occurring before the age of 55 years. Notably, 23.97% of deaths occurred within the sixth decade of life. Stratification by five-year age groups revealed significantly elevated SMRs within the 50-64.9-year age strata. This finding concurs with observations from comparable international studies examining asbestos-exposed populations.[38-40] Notably, Markowitz et al. (2013), in their study of chrysotile-exposed North American insulators, reported similar findings with 50% of the cohort reaching the age of 65 years, and one-third of deaths occurring during their sixth decade.[39]

In contrast to findings reported in existing literature, this study revealed a significant sex-specific disparity in SMRs relative to the general population.. The absence of significant excess mortality among male asbestos miners within this cohort deviated from the elevated mortality rates reported in other asbestos-exposed male populations.[13,38] This discrepancy may be attributable to survivorship bias.

While no significant excess mortality was observed among males relative to the general population, a significantly elevated excess mortality of 17% was evident among females. This disparity may in part be attributed to the significantly higher proportion of female employment in aboveground settings within this cohort (96.3% in females compared to 71.5% in males). Aboveground settings were typically associated with job tasks involving more intense asbestos exposure.[23] For example, women were often engaged in cobbing, which entailed the breaking down of asbestos rock into ore by hand.[20] Additional domestic exposure when laundering asbestos-contaminated clothes may also have contributed to greater exposures.

Notably, most female cases of mesothelioma (48/49), lung cancer (5/5), non-malignant ARD 1 (355/376), and ARD 2 (37/42) in this cohort occurred in aboveground workers, suggesting higher cumulative fibre exposure in these settings (Table SVI: Supplementary information). Furthermore, a substantial proportion of females in aboveground settings were either directly exposed to crocidolite asbestos (34.7%) or had unspecified exposure histories (54.9%), the latter potentially including crocidolite exposure (Table SVII: Supplementary Information). Overall, these findings highlight the importance of gendered exposure pathways in asbestos-related disease research and suggest that higher aboveground crocidolite asbestos exposure was a key driver of asbestos-related mortality amongst females relative to the general population. However, the influence of other unexamined factors on mortality risk (e.g., comorbidities) cannot be disregarded.

What time trends in excess mortality were identified?

While the overall excess mortality for the entire observation period was only marginally elevated at 4%, a temporal analysis of SMRs revealed varying trends with distinct periods of excess mortality. Specifically, the cohort of former miners exhibited an initial period of increasing mortality from 2004 to 2010. This was followed by a period of relative stability in excess mortality between 2011 and 2018. Barring a discrete, COVID-19-related elevation in 2021, a downward trend in SMRs was evident from 2019 onwards.

Based on the industry's zenith in the 1970s and the characteristic latency between asbestos exposure and the manifestation of related diseases, the observed pattern is consistent with the characteristic latency period for asbestos-related diseases (ARD). The pattern, which entailed a gradual increase in excess mortality ratios, culminating in a plateau approximately four decades after peak exposure followed by a subsequent decline, aligns temporally with the latency period. The subsequent decrease in SMRs from 2019 onward may suggest a potential attenuation of the long-term health sequelae associated with historical asbestos exposure within this specific cohort of former miners.

Which predictors of mortality were identified?

A key aspect of this study was the identification of mortality predictors. Consistent with prior research, significant demographic risk factors included age (specifically exceeding 55 years), male sex, and a positive smoking history.[10-12, 41-46] Occupational factors demonstrated a more limited predictive capacity, with only the nature of mine work (aboveground vs underground) exhibiting a significant association with mortality outcomes. Clinical predictors of mortality included the ILO profusion category, which demonstrated the strongest association. Other significant clinical predictors included underweight status, lung function and the ARD category as assigned by the SOMP.

While research has demonstrated strong links between occupational factors such as cumulative exposure, exposure duration, fibre type and dimensions, and asbestos-related mortality,[9,47-60] this study identified employment exclusively aboveground relative to underground as the only statistically significant occupational predictor. As noted earlier, aboveground work was generally associated with higher intensities of airborne asbestos fibre exposure.[20,23] For example, milling and bagging of asbestos were aboveground asbestos mining tasks associated with high fibre exposures of up to 57 fibres/ml in the Northern Cape during the 1960s.[23] By contrast, underground mining in South Africa often occurred in wet conditions, which suppressed the aerosolisation and subsequent inhalation of asbestos fibres, potentially mitigating disease risk.

Unexpectedly, there was no exposure-response association between time in employment and mortality in this cohort. While miners employed for over 15 years demonstrated an increased mortality risk, this was not statistically significant. Several factors may have contributed to this unanticipated finding. Firstly, significant limitations in exposure assessment were apparent. The high proportion of participants with less than five years of employment (67.4%), coupled with a substantial amount of missing data (23.8%) for time in employment, creates the potential for substantial misclassification. Furthermore, the practice of short-term employment in the mining industry, combined with the reliance on subjective reporting of exposure by participants and difficulties in obtaining complete occupational histories, further complicates accurate exposure assessment. Misclassified time in employment is therefore likely to have obscured the true dose-response relationship between occupational asbestos exposure and mortality.

Secondly, in the absence of data on asbestos fibre exposures, cumulative exposure was not measurable. High-intensity exposure within short periods could result in substantial cumulative asbestos burden even in those with shorter employment durations. Moreover, para-occupational and environmental exposures, because of residential proximity to mining operations, could have resulted in a significant underestimation of asbestos exposure. Thirdly, the healthy worker effect may have played a role. Individuals with pre-existing health conditions may be less likely to be hired for or retain employment in physically demanding mining jobs. If these individuals were predominantly employed for short periods, they could contribute to the higher mortality observed in the less than five-year exposure group. Finally, the small number of participants in the more than 15-year exposure group (0.7%) may have limited the study's power to detect a statistically significant difference in mortality in this subgroup.

In addition, this study found no statistically significant association between the type of asbestos fibre exposure and mortality risk. However, the asbestos exposure type was unspecified for 33.1% of the cohort. More importantly, increased mortality was observed within this subgroup (aHR=1.21; 95% CI: 1.10-1.32). Based on data released by the Trusts in 2006, most claimants (70.6%) were employed on crocidolite mines in the Northern Cape.[23] It is thus plausible that within the unspecified category, a significant proportion of workers were exposed to more hazardous crocidolite fibre types, accounting for the higher mortality observed. The absence of exposure data for many participants is likely due to non-standardised capture of data.

Analysis of the relationship between type of fibre exposure and ARD category revealed that 45.9% of participants diagnosed with asbestos-related lung cancer and mesothelioma (ARD 3 and ARD 4) were crocidolite-exposed, 22.2% were chrysotile-exposed and 0.7% amosite-exposed. The possibility exists that amongst the 31.3% of participants with unspecified exposure, a significant proportion of participants were exposed to crocidolite, given the Trusts' reports of higher prevalence of crocidolite exposure amongst claimants.[23] This observation is consistent with existing research suggesting a greater carcinogenic potential associated with crocidolite fibres.[51] Hodgson et al. (2000) demonstrated a differential mesothelioma risk across chrysotile, amosite, and crocidolite fibres in an approximate ratio of 1:100:500 and differential lung cancer risk between chrysotile and amphibole fibres of 1:10 to 1:50.[51]

This study demonstrated a significant association between underweight status and increased mortality. Several potential mechanisms may underlie this observation. Underweight may be associated with reduced physiological reserves and compromised immune function, potentially exacerbating disease progression and increasing mortality risk.[61] Notably, underweight status is a known risk factor for tuberculosis, which is highly prevalent in South Africa and may independently have contributed to increased mortality in this population.[62]

The strong predictive ability of CXR findings on mortality outcomes in this asbestos-exposed mining cohort was established. The presence of radiological opacities as per ILO profusion classification and costophrenic angle obliteration were found to be significant predictors of mortality, with ILO profusion category 3 demonstrating the strongest association. These findings not only affirm the ILO classification system's validity in risk stratification but also emphasise the useful role of ILO-standardised CXR interpretation for surveillance. The findings are consistent with prior research, which focused on the description of radiological manifestations associated with ARD [63,64] and studies which reported ILO profusion category as a strong predictor of mortality in asbestos-exposed cohorts.[39, 65]

Despite representing a small proportion of the cohort (1.74%), elevated mortality rates were observed for ILO profusion categories 2 and 3 in a grade-responsive manner. This suggests the potential for rapid disease progression and/or the development of severe complications, impacting disease burden and highlighting the increased healthcare needs of these high-risk individuals. Although less pronounced, the mortality risk associated with ILO profusion category 1 was still appreciable (aHR=1.13). This possibly reflects the known limitation of CXRs in estimating parenchymal asbestosis due to suboptimal sensitivity. Asbestosis has been shown to be present even with normal radiographic findings.[66,67]

Both diffuse pleural thickening and costophrenic angle obliteration demonstrated an increased hazard of death, although the former did not reach statistical significance. Diffuse pleural thickening, defined by the ILO Classification as visceral pleural thickening exceeding 3mm in width in the presence of and in continuity with costophrenic angle obliteration,[29] is a marker of more significant asbestos-related injury.[68] It is associated with restrictive lung impairment and an elevated risk of developing more severe asbestos-related disease.[68] In this cohort, 66.8% of participants exhibiting diffuse pleural thickening had low FVC z-scores, with 58.2% demonstrating moderately to severely reduced FVC z-scores (i.e., below -2.0). This impaired lung function likely contributed to the observed increased mortality risk within this subgroup (**Figure 3**). Furthermore, diffuse pleural thickening was observed in 7.2% of mesothelioma cases within this cohort.

Costophrenic angle obliteration without concurrent diffuse pleural thickening was present in 7.2% of the study population. Costophrenic angle obliteration in asbestos-exposed workers is often associated with pleural fibrosis or pleural effusions, which may be benign or malignant.[68,69] Approximately 56.7% of the cohort with costophrenic angle obliteration had an abnormally low FVC z-score, and of these, 47.9% demonstrated a moderately to severely reduced FVC z-score (i.e., below -2.0). The abnormal lung function may have contributed to the increased hazard of death observed in this subset (**Figure 4**). In addition, 7.2% of participants classified as having asbestos-related cancer or mesothelioma (ARD 3 or ARD 4) exhibited costophrenic angle obliteration, suggesting the possibility of malignant effusions, which could further contribute to the predicted increased mortality risk.

Impaired lung function, operationalised as low FEV_1 and FVC z-scores, significantly and independently predicted mortality, with FEV_1 z-score demonstrating a stronger prognostic ability. A threshold effect was demonstrated at moderately low levels for FEV_1 and severely low for FVC z-scores. Prior research has established dose-responsive associations between impaired pulmonary function and increased mortality risk.[70,71]

In addition, a negative correlation between increasing ILO profusion category and FEV_1- or FVC z-scores was observed (Table SV and Figure S4: Supplementary information). Miller et al. (2013) reported similar findings.[72] Given the correlation between radiological severity and lung function impairment, medical surveillance should include CXR and spirometry to enable early identification of abnormal lung function.

A statistically significant association between ARD category severity as per SOMP classification and the hazard of death was observed. As anticipated, an elevated hazard of mortality was observed in participants with parenchymal asbestosis and/or asbestos-related pleural disease and impaired lung function. In addition, asbestos-related lung cancer and mesothelioma (ARD 3 and ARD 4, respectively) were associated with sharply increased mortality hazards. These observations appear to validate the Trusts' ARD classification system. However, the Trusts' use of ECSC reference values to determine the difference between ARD categories 1 and 2 warrants consideration. ECSC reference values are primarily derived from Caucasian populations and may not account for differences in ethnicity, occupational exposures,[23] environmental and occupational factors prevalent in African populations.[30] Furthermore, participants' lung function was assessed using the ECSC reference values without applying the "correction factors" that were recommended by the South African Thoracic Society guidelines at the time.[73] The omission of these correction factors may have influenced the categorisation of individuals into ARD categories 1 and 2. As a result, the use of ECSC reference values in this cohort could have led to misclassification of lung function status and inaccurate evaluation of respiratory impairment caused by occupational lung disease, potentially affecting eligibility for compensation. In response to such concerns, the ERS/ATS has since recommended the use of the GLI reference equations, employed in this study, as a more appropriate standard for lung function assessment.[74] It is important to note, however, that the GLI reference equations were not yet available in 2004, when the first cases were evaluated.

Study limitations

This retrospective cohort study, utilising secondary data, is subject to several limitations that may affect the validity and generalisability of its findings. The historical fragmentation and inaccuracy of the South African death registration system raises concerns about the completeness of death reporting.[33] While significant improvements have been made, the possibility of missed deaths and consequent underestimation of mortality rates cannot be disregarded.[33] Furthermore, the absence of cause-of-death and morbidity data prevents attribution of mortality to specific asbestos-related diseases within this cohort.

The interpretation of mortality trends was constrained by variations in participants' entry times into the study and the differing circumstances surrounding their inclusion. A key methodological challenge involved determining an appropriate start date for survival time. Due to the lack of accurate and complete records on participants' employment start dates, researchers opted to use the date of entry onto the study database, which was reliably documented for all participants. However, this date may not accurately represent the point at which individuals became at risk for the outcome of interest (i.e., mortality), potentially introducing bias into survival estimates. In addition, researchers calculated CMRs as rates, i.e. observed deaths per person-years for each calendar period, rather than using a clearly defined population at risk. This approach accounts for varying entry times and follow-up durations. However, it may obscure the actual timing and composition of risk, potentially leading to biased estimates. Without a well-defined denominator population, mortality rates can be either diluted or inflated due to differences in follow-up time and the potential for survivor bias. This also limits the accuracy of comparisons across calendar periods.

Although quality control measures were employed by the Trusts where possible (**Table I**), the potential for information bias resulting from transcription and measurement errors of predictor variables still exists. For example, the SOMP evaluators' knowledge of participant history during CXR interpretation could have introduced assessment bias in the reading of the CXR and ARD classification. Furthermore, no accurate quantitative data on the exposure intensity and hence cumulative dose of exposure were available. While the duration of exposure is often considered a key predictor of adverse asbestos-related health outcomes, the absence of precise data on intensity makes misclassification likely. Survival bias may exist as older miners with potentially higher early-life exposures may have died before the database's inception in 2003, resulting in the underestimation of the overall mortality rate. The study's focus on predominantly crocidolite-exposed South African miners necessitates caution when extrapolating findings to asbestos mining populations in neighbouring countries where chrysotile asbestos was mined, notably Eswatini and Zimbabwe.

6. CONCLUSION

This study presents novel insights into the long-term mortality experience of former South African asbestos miners, a historically marginalised and underrepresented occupational group.[75] By focusing on overall mortality trends and associated clinical predictors, it contributes to a better understanding of the enduring health consequences of asbestos exposure in the post-employment phase. The findings must be understood within the broader context of systemic inequality, where inadequate workplace protections and persistent disparities in healthcare access, particularly in historically disadvantaged provinces, have compounded health risks for this population.[75]

Post-employment medical surveillance of asbestos-exposed workers remains essential but poses significant challenges due to limited resources, wide geographic dispersion, poor awareness of risk, and restricted access to appropriate healthcare services. Addressing these barriers requires a multipronged approach that includes targeted allocation of resources, enhanced diagnostic capacity, increased awareness, improved accessibility, and incentives for case finding. Training healthcare providers to better support this population is also critical to delivering effective surveillance and care.

Although curative treatment for asbestos-related diseases remains limited, there is clear potential to improve health-related quality of life through supportive care. Preventive and clinical strategies such as timely management of respiratory complications, targeted vaccination programmes (e.g., pneumococcal, influenza, COVID-19), and smoking cessation support could help preserve lung function and attenuate the progression of asbestos-related complications. These approaches are particularly important given the challenges of modifying the progression of underlying pathologies associated with asbestos exposure.

While this study did not directly assess the role of compensation systems or social security structures, the broader context highlights the importance of ensuring equitable access to such support. Initiatives aimed at improving awareness of statutory rights, simplifying claims processes, providing administrative assistance, increasing compensation awards to align with inflation, and facilitating access to social security provisions may help mitigate some of the long-term socioeconomic and health consequences experienced by former miners. These areas warrant further empirical investigation.

Collectively, these efforts have the potential to inform more targeted clinical interventions and evidence-based policies, ultimately contributing to the reduction or postponement of preventable mortality and the improvement of long-term health outcomes for this historically disadvantaged workforce affected by occupational asbestos exposure in South Africa.

Future research should aim to 1) develop and validate a clinical risk stratification tool using demographic, radiological, and spirometric markers to support early identification of high-risk individuals; 2) investigate the role of co-morbidities such as tuberculosis in shaping mortality outcomes within this exposed population and 3) explore longitudinal trajectories of lung function and radiological progression to better understand disease evolution and inform customised intervention strategies.

MANUSCRIPT TABLES AND FIGURES

Table I: Operationalisation of variables and quality control measures employed

Predictor variable	Variable definition	Quality control measures
Cigarette Smoking History	**Never:** Never smoked/smoked < 1 pack year. **Previous**: Smoked > 1 pack year but stopped **Current:** Still smoking at present.	
Body Mass Index (kg/m^2)	BMI was calculated as weight/height^2 (kg/m^2) and categorised as: **Underweight**: < 18.5 kg/m^2 **Normal:** = 18.5 to 24.9 kg/m^2 **Overweight:** = 25 to 29.9 kg/m^2 **Obese:** ≥ 30 kg/m^2	Weight and height measurements were performed in standardised manner**.**
Radiological data ILO Profusion categories	Radiological data were reported in a standardised manner by a radiologist and occupational medicine specialist trained in reading radiographs in accordance with the International Labour Organisation (ILO) International Classification of Radiographs of Pneumoconioses.[26] ILO Profusion Categories: **Category 0:** 0/-; 0/0/; 0/1 **Category 1:** 1/0; 1/1; 1/2 **Category 2:** 2/1; 2/2; 2/3 **Category 3:** 3/2; 3/3; 3/+ Category 1-3 were considered abnormal	Trained radiologists and medical practitioners with experience and expertise in occupational medicine were members of a Specialist Occupational Medicine Panel (SOMP) who captured clinical data. The radiographs were read with full knowledge of the patient's medical, occupational, or cigarette-smoking history. The classification of radiological data was done by consensus between the radiologist and the occupational medicine practitioner, with a tendency for the radiologist's reading to prevail. Where classification was difficult or borderline, or where there was disagreement between the radiologist and occupational medicine specialist, a different SOMP panel was enlisted to classify the CXR. In such cases, the report of the SOMP panel making the higher classification was used.
Spirometry Classification FEV_1 Normal FEV_1 Low FVC Normal FVC Low	 **FEV_1 Normal:** FEV_1 z-score ≥ -1.64 **FEV_1 Low:** FEV_1 z-score < -1.64 **Mild:** FEV_1 z-score: < -1.64 but > -2.0 **Moderate:** FEV_1 z-score: ≤ -2.0 but > -3.0 **Severe:** FEV_1 z-score: ≤ -3.0 **FVC Normal:** FVC z-score ≥ -1.64 **FVC Low:** FVC z-score < -1.64 **Mild:** FVC z-score: < -1.64 but > -2.0 **Moderate:** FVC z-score: ≤ -2.0 but > -3.0 **Severe:** FVC z-score: ≤ -3.0	Global Lung Function Initiative (GLI) reference equations were used to generate FEV_1, FVC and FEV_1/FVC z-scores for each participant using their age, sex, height and raw FEV_1 and FVC values. The GLI-other ethnic category was used. A z-score cut-off ≥ -1.64 was used to dichotomise the FEV_1 and FVC raw values into normal and low categories. The GLI z-scores were additionally used to further subcategorise FEV_1 and FVC as outlined.

Predictor variable	Variable definition	Quality control measures
Asbestos-Related Disease (ARD) Category No ARD ARD 1 ARD 2 ARD 3 ARD 4 ARD not determined yet	The Trusts used a composite classification system to categorise asbestos-related disease (ARD) in claimants. Both the radiological findings as per ILO classification and the spirometry results using the European Community for Steel and Coal (ECSC) reference values were used to categorise the claimants as follows:[27] **No ARD:** Spirometry: FEV_1 and FVC ≥ 80% FEV_1/FVC ratio ≥ 75% Radiological: No evidence of asbestosis/asbestos-related changes **ARD 1**: Asbestos-related pleural thickening/asbestosis with mild to moderate lung function impairment Spirometry: FEV_1 and FVC ≥ 52% but < 80% FEV_1/FVC ratio ≥ 55% but < 75% Radiological: ILO reading consistent with asbestosis/asbestos-related changes **ARD 2:** Asbestos-related pleural thickening/asbestosis with severe lung function impairment Spirometry: FEV_1 and FVC < 52% FEV_1/FVC ratio < 55% Radiological: ILO reading consistent with asbestosis/asbestos-related changes **ARD 3:** Asbestos-related Lung cancer Based on histological evidence **ARD 4:** Mesothelioma Based on histological evidence For ARD 3 and 4, where histological evidence was not available, radiological diagnosis was made by a radiologist. Where asbestosis or pleural disease coexisted with malignancy, the higher ARD grade was used.	

Characteristic	Total	Alive	Deceased	p-value	Crude Mortality Rate (/1000 person-years)
Table II: **Demographic, occupational and clinical characteristics of Asbestos and Kgalagadi Relief Trust claimants with crude mortality rates for period 2004 to 2023**					
Overall	11 343	6 237 (55.0%)	5 106 (45.0%)	-	37.4
Age on Entry to Cohort (years)	57 (0.5%)				
	1 852 (16.3%)			0.000	
*< 35	4 393 (38.7%)	43 (0.4%)	14 (0.1%)		16.3
35 – 44.9	3 015 (26.6%)	1 279 (11.4%)	563 (5.0%)		21.3
45 - 54.9	2 026 (17.9%)	2 739 (24.2%)	1 654 (14.6%)		28.3
55 – 64.9		1 449 (12.8%)	1 566 (13.8%)		47.0
≥ 65		717 (6.3%)	1 309 (11.5%)		72.3
Biological Sex					
*Female	1 955 (17.2%)	1 133 (10.0%)	822 (7.3%)	0.004	33.0
Male	9 388 (82.8%)	5 104 (45.0%)	4 284 (37.8%)		37.9
Cigarette Smoking Status					
*Never	7 763 (68.4%)	4 558 (40.2%)	3 205 (28.3%)	0.000	33.7
Previous	3 580 (31.6%)	1 679 (14.8%)	1 901 (16.8%)		45.4
Type of Asbestos Exposure					
*Chrysotile only	2 338 (20.6%)	1 265 (11.2%)	1 073 (9.5%)	0.000	39.4
Crocidolite only	4 892 (43.1%)	2 741 (24.1%)	2 151 (19.0%)		35.5
Amosite	278 (2.5%)	201 (1.8%)	77 (0.7%)		20.3
Mixed	81 (0.7%)	34 (0.3%)	47 (0.4%)		49.1
Unspecified	3 754 (33.1%)	1 996 (17.6%)	1 758 (15.5%)		39.5
Nature of Mine Work					
*Underground only	2 506 (22.1%)	1 412 (12.5%)	1 094 (9.6%)	0.299	36.0
Aboveground only	8 592 (75.8%)	4 692 (41.4%)	3 900 (34.4%)		37.5
Unspecified	245 (2.2%)	133 (1.2%)	112 (1.0%)		41.0
Time in Employment (years)					
*0 - 5	7 649 (67.4%)	4 177 (36.8%)	3 472 (30.6%)	0.257	38.1
5 - 10	803 (7.1%)	462 (4.1%)	341 (3.0%)		33.5
10 -15	138 (1.2%)	83 (0.7%)	55 (0.5%)		30.8
>15	76 (0.7%)	37 (0.3%)	39 (0.3%)		44.9
Unspecified	2 677 (23.6%)	1 478 (13.0%)	1 199 (10.6%)		36.1
BMI at Baseline (kg/m^2)					
*Normal	5 305 (50.2%)	3 022 (26.6%)	2 283 (20.1%)	0.000	35.1
Underweight	1 651 (15.6%)	668 (5.9%)	983 (8.7%)		57.5
Overweight	2 192 (20.8%)	1 360 (12.0%)	832 (7.3%)		29.6
Obese	1 415 (13.4%)	850 (7.5%)	565 (5.0%)		31.9
Unspecified	780 (6.9%)	337 (3.0%)	443 (3.9%)		48.8
ILO Profusion Category					
* Category 0	8 981 (79.2%)	5 198 (45.8%)	3 783 (33.4%)	0.000	34.2
Category 1	2 166 (19.1%)	972 (8.6%)	1 194 (10.5%)		48.0
Category 2	166 (1.5%)	60 (0.5%)	106 (0.9%)		71.8
Category 3	30 (0.3%)	7 (0.1%)	23 (0.2%)		108.3
Pleural Plaques					
*Absent	8 135 (71.7%)	4 491 (39.6%)	3 644 (32.1%)	0.452	37.1
Present	3 208 (28.3%)	1 746 (15.4%)	1 462 (12.9%)		37.7

Characteristic	Total	Alive	Deceased	p-value	Crude Mortality Rate (/1000 person-years)
Costophrenic angle obliteration					
*Absent	10 522 (92.8%)	5 917 (52.2%)	4 605 (40.6%)	0.000	35.9
Present	821 (7.2%)	320 (2.8%)	501 (4.4%)		57.0
Diffuse Pleural Thickening					
*Absent	10 758 (94.8%)	6023 (53.1%)	4 735 (41.7%)	0.000	36.1
Present	585 (5.2%)	214 (1.9%)	371 (3.3%)		61.7
FEV_1 z-score (litres)					
*Normal	6 311 (60.0%)	3 814 (36.3%)	2 497 (23.8%)	0.000	32.6
#Low	4 202 (40.0%)	2 053 (19.5%)	2 149 (20.4%)		44.3
Mild	1 116 (10.6%)	639 (6.1%)	477 (4.5%)		34.2
Moderate	2 034 (19.4%)	1 017 (9.7%)	1017 (9.7%)		41.6
Severe	1 052 (10.0%)	397 (3.8%)	655 (6.2%)		65.2
Unspecified	830 (7.3%)	370 (3.3%)	460 (4.1%)		47.6
FVC z-score (litres)					
*Normal	6 544 (62.3%)	3 941 (37.5%)	2 603 (24.8%)	0.000	31.9
#Low	3 969 (37.8%)	1 926 (18.3%)	2 043 (19.4%)		44.5
Mild	940 (8.9%)	527 (5.0%)	413 (3.9%)		35.2
Moderate	1 788 (17.0%)	934 (8.9%)	854 (8.1%)		39.7
Severe	1 241 (11.8%)	465 (4.4%)	776 (7.4%)		61.6
Unspecified	830 (7.3%)	370 (3.3%)	460 (4.1%)		47.6
Asbestos-related Disease (ARD) Category					
*No ARD	7 154 (63.1%)	4 429 (39.1%)	2 725 (24.0%)	0.000	30.5
ARD 1	3 284 (29.0%)	1 580 (13.9%)	1 704 (15.0%)		42.6
ARD 2	377 (3.3%)	102 (0.9%)	275 (2.4%)		82.0
ARD 3	44 (0.4%)	0 (0.0%)	44 (0.4%)		107.1
ARD 4	263 (2.3%)	15 (0.1%)	248 (2.2%)		152.3
Not determined	221 (2.0%)	111 (1.0%)	110 (1.0%)		48.2

*Reference category

*Normal FEV_1: FEV_1 z-score ≥ -1.64
#Low FEV_1: FEV_1 z-score ≤ -1.64
Mild: FEV_1 z-score: -1.64 to -2.0
Moderate: FEV_1 z-score: -2.0 to -3.0
Severe: FEV_1 z-score: ≤ -3.0

Normal FVC: FVC z-score ≥ -1.64
#Low FVC: FVC z-score ≤ -1.64
Mild: FVC z-score: -1.64 to -2.0
Moderate: FVC z-score: -2.0 to -3.0
Severe: FVC z-score: ≤ -3.0

ARD categories defined in Table I

Table III: Demographic, occupational and clinical predictors of mortality in Asbestos and Kgalagadi Trust claimants between 2004 and 2023			
Predictor	**#Adjusted Hazard Ratio**	**95% CI**	**p-value**
Age on Entry to Cohort (years)			
* <35	-	-	-
35 – 44.9	1.15	0.68 – 1.96	0.598
45 - 54.9	1.50	0.89 – 2.55	0.129
55 - 64.9	2.60	1.54 – 4.41	0.000
≥ 65	4.46	2.63 – 7.58	0.000
Biological Sex			
*Female	-	-	-
Male	1.20	1.10– 1.31	0.000
Cigarette Smoking Status			
*Never	-	-	-
Previous	1.43	1.35 – 1.53	0.000
Type of Asbestos Exposure			
*Chrysotile only	-	-	-
Crocidolite only	1.08	1.00 – 1.17	0.058
Amosite only	0.75	0.59 – 0.96	0.022
Mixed	1.14	0.83 – 1.57	0.414
Unspecified	1.21	1.10 – 1.32	0.000
Nature of Mine Work			
*Underground only	-	-	-
Aboveground only	1.16	1.07 – 1.25	0.000
Unspecified	1.05	0.85 – 1.30	0.653
Time in Employment (years)			
*0 - 5	-	-	-
5 - 10	0.85	0.75 – 0.96	0.007
10 -15	0.81	0.62 – 1.08	0.147
>15	1.27	0.91 – 1.76	0.157
Unknown	1.06	0.98 – 1.15	0.165
BMI at baseline (kg/m^2)			
*Normal	-	-	-
Underweight	1.46	1.35 – 1.58	0.000
$Overweight	0.89	0.82 – 0.97	0.006
$Obese	1.03	0.93 – 1.13	0.609
ILO Profusion Categories			
*Category 0	-	-	-
Category 1	1.13	1.05 – 1.23	0.002
Category 2	1.23	1.00 – 1.51	0.054
Category 3	2.34	1.52 – 3.58	0.000
Pleural Plaques			
*Absent	-	-	-
Present	0.85	0.79 – 0.92	0.000

Predictor	Adjusted Hazard Ratio	95% CI	p-value
Costophrenic angle obliteration			
*Absent	-	-	-
Present	1.27	1.14 – 1.41	0.000
$Diffuse Pleural Thickening			
*Absent	-	-	-
Present	1.13	0.99 – 1.28	0.061
FEV_1 z-score			
*Normal	-	-	-
#Low			
Mild	1.02	0.92 – 1.13	0.712
Moderate	1.13	1.02 – 1.24	0.014
$Severe	1.60	1.41 – 1.81	0.000
FVC z-score			
*Normal	-	-	-
#Low			
Mild	1.06	0.95 – 1.18	0.302
Moderate	1.06	0.97 – 1.17	0.220
Severe	1.26	1.12 – 1.42	0.000
Asbestos-Related Disease (ARD) Category			
*No ARD	-	-	-
ARD 1	1.14	1.04 – 1.25	0.004
ARD 2	1.16	0.98 – 1.37	0.076
ARD 3	3.85	2.47 – 6.01	0.000
ARD 4	6.35	5.42 – 7.45	0.000
Not determined	1.37	1.10 – 1.70	0.005

*Reference category

*Normal FEV_1: FEV_1 z-score: ≥ -1.64	Normal FVC: FVC z-score: ≥ -1.64
#Low FEV_1: FEV_1 z-score: ≤ -1.64	Low FVC: FVC z-score: ≤ -1.64
Mild: FEV_1 z-score: -1.64 to -2.0	Mild: FVC z-score: -1.64 to -2.0
Moderate: FEV_1 z-score: -2.0 to -3.0	Moderate: FVC z-score: -2.0 to -3.0
Severe: FEV_1 z-score: ≤ -3.0	Severe: FVC z-score: ≤ -3.0

#Hazard ratios adjusted for all covariates

$Covariates and specific levels of covariates which violated the proportional hazards assumption and were modelled in an Extended Cox Regression Model (see Supplementary information)

Table IV: Standardised mortality ratios (SMRs) of Trust claimants relative to the general South African population standardised by sex, age and calendar year

Sex	Observed Deaths	Expected Deaths	*SMR	95% CI
Male	4 284	4200	1.02	0.99 – 1.05
Female	822	702	1.17	1.09 – 1.25
Age (years)	**Observed Deaths**	**Expected Deaths**	**SMR**	**95% CI**
<30	0	0	0	-
30-34.9	1	3	0.33	-0.32 – 0.99
35-39.9	25	29	0.86	0.52 – 1.20
40-44.9	118	120	0.98	0.81 – 1.16
45-49.9	282	286	0.98	0.87 – 1.10
50-54.9	544	476	1.14	1.05 – 1.24
55-59.9	680	676	1.01	0.93 – 1.08
60-64.9	835	753	1.14	1.03 – 1.18
≥65	2621	2 559	1.02	0.99 – 1.06
Calendar year	**Observed Deaths**	**Expected Deaths**	***SMR**	**95% CI**
2004	11	13	0.85	0.35 – 1.35
2005	54	60	0.90	0.66 – 1.14
2006	178	162	1.10	0.94 – 1.26
2007	239	208	1.15	1.00 – 1.29
2008	285	227	1.26	1.11– 1.40
2009	297	248	1.20	1.06 – 1.33
2010	335	260	1.29	1.15 – 1.43
2011	293	261	1.12	0.99 – 1.25
2012	286	260	1.10	0.97 – 1.23
2013	273	262	1.04	0.92 – 1.17
2014	301	266	1.13	1.00 – 1.26
2015	306	272	1.13	1.00 – 1.25
2016	317	278	1.14	1.01 – 1.27
2017	296	283	1.05	0.93 – 1.17
2018	318	292	1.09	0.97 – 1.21
2019	241	329	0.73	0.64 – 0.83
2020	296	385	0.77	0.68 – 0.86
2021	467	439	1.06	0.97 – 1.16
2022	264	328	0.80	0.71 – 0.90
till 21/03/2023	49	69	0.71	0.51 – 0.91
Total	**5106**	**4 902**	**1.04**	**1.01 – 1.07**

*SMR: Standardised Mortality Ratio

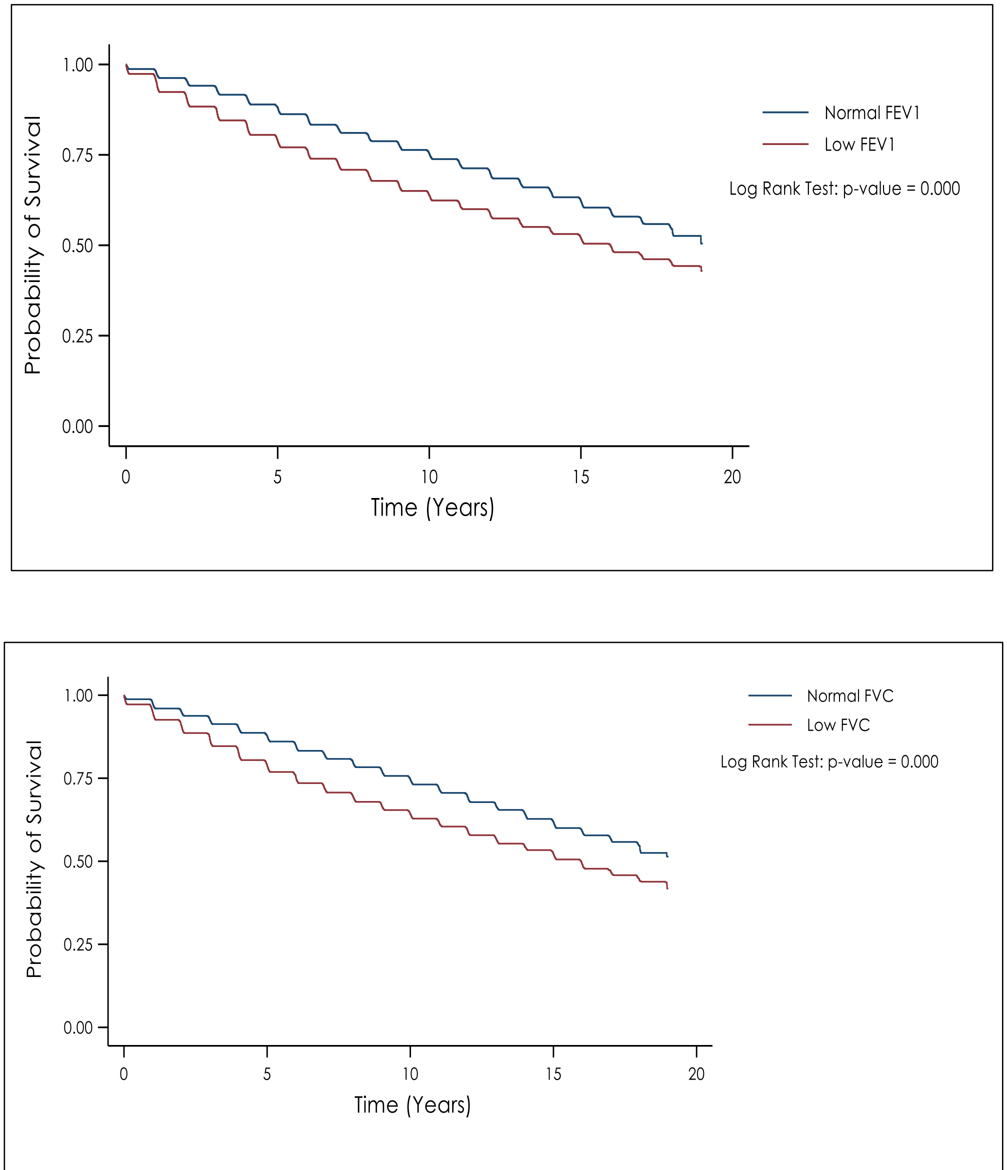
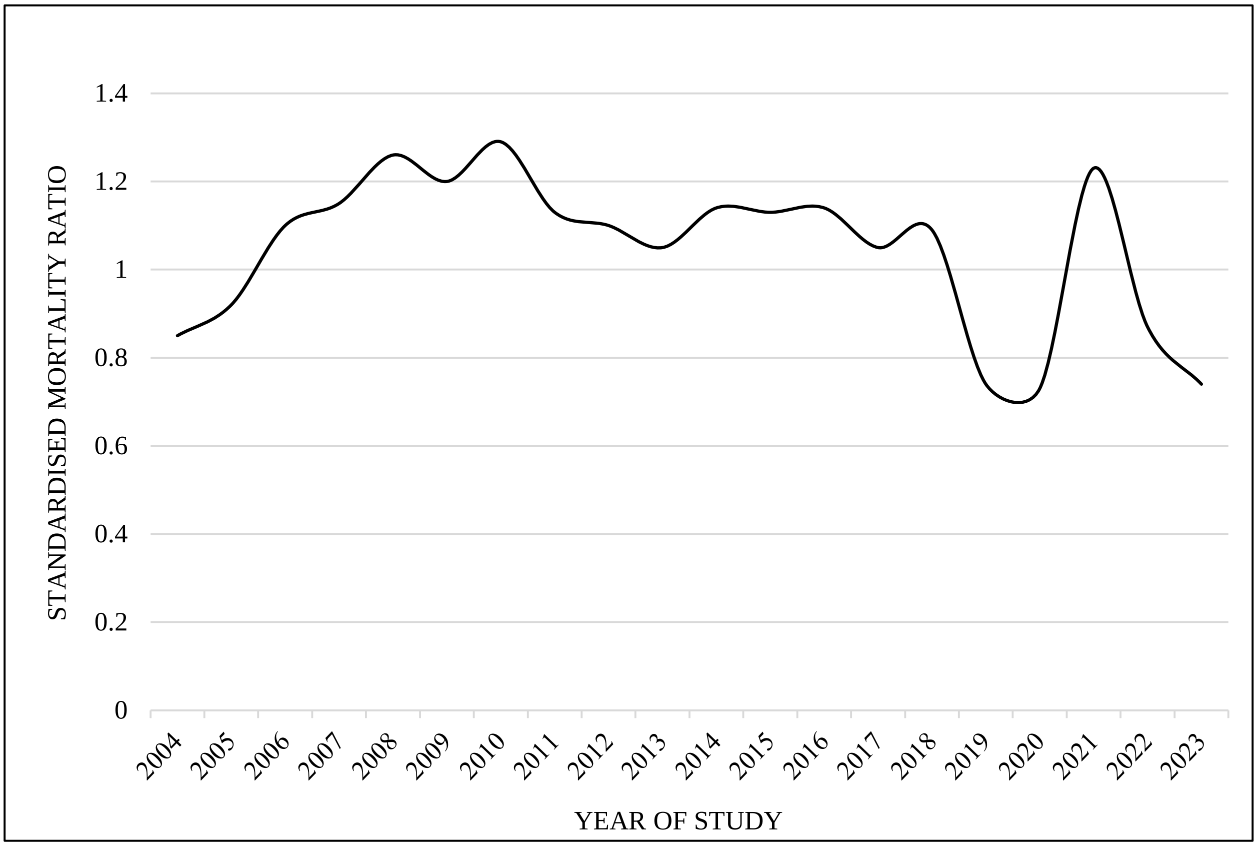


Figure 1: Kaplan-Meier plot comparing the survival probability between participants with and without a low FEV_1 z-score or FVC z-score



<u>Figure 2</u>: Standardised mortality ratio among Asbestos and Kgalagadi Relief Trust claimants for each year of the study period from 2004 to 2023

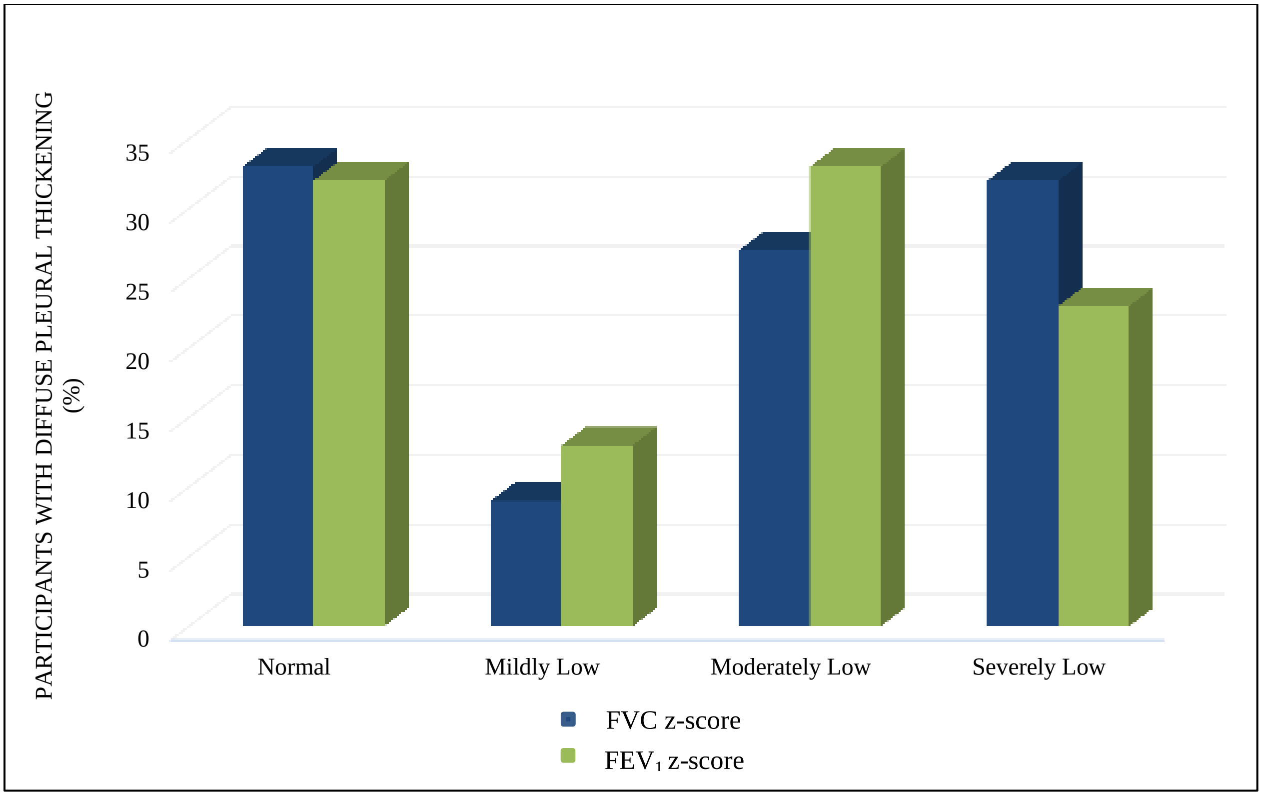


Figure 3: Spirometry findings in participants with diffuse pleural thickening

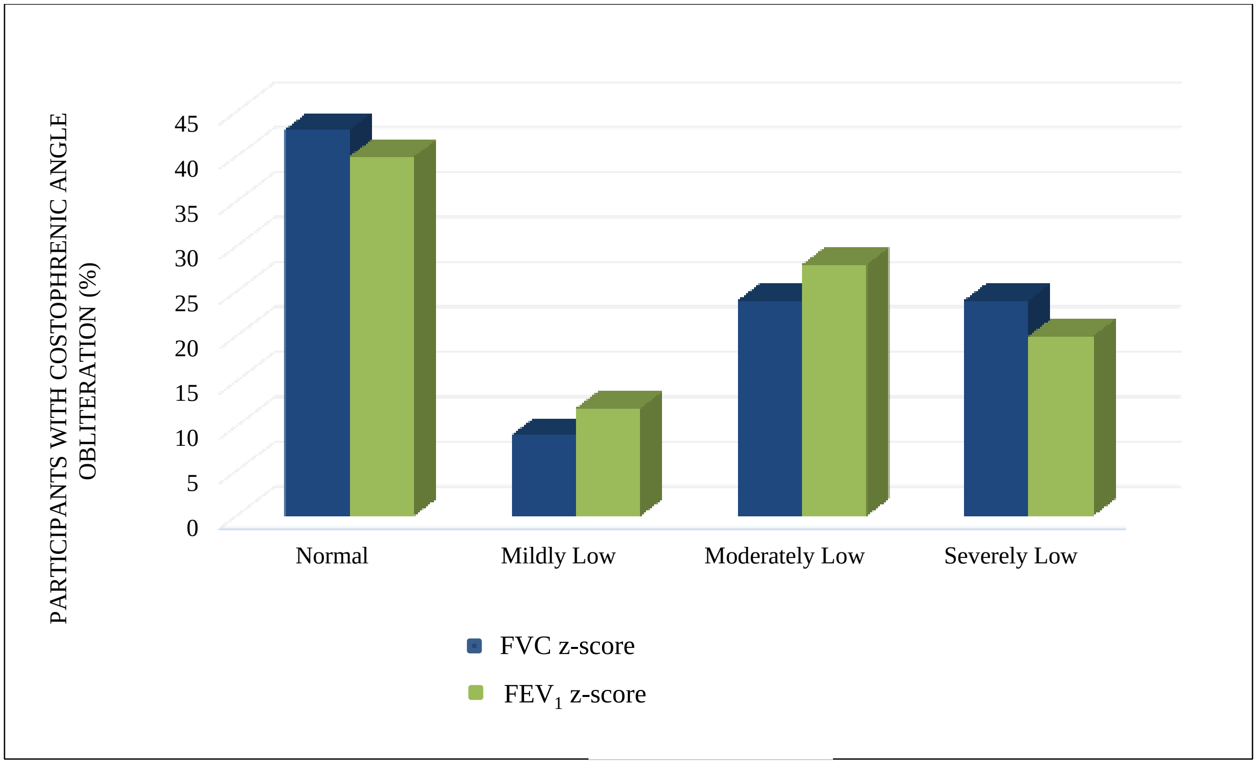


Figure 4: Spirometry findings in participants with costophrenic obliteration

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SECTION III: APPENDICES

Appendix 1: Research Protocol

An evaluation of mortality rates and their determinants in a cohort of former asbestos-exposed miners

A MMed (Occupational Medicine) Dissertation Research Proposal by

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1. ABBREVIATIONS/ACRONYMS

AHR:	Adjusted Hazard Ratio
ARD:	Asbestos-related disease
ART:	Asbestos Relief Trust
ASSA:	Actuarial Society of South Africa
ATS:	American Thoracic Society
BMI:	Body mass index
COPD:	Chronic Obstructive Pulmonary Disease
ECCS:	European Community of Coal and Steel
ERS:	European Respiratory Society
FEV_1/FVC ratio:	Forced expiratory volume/Forced vital capacity ratio
FEV_1:	Forced expiratory volume exhaled in 1 minute
Fibre/ml-year:	Fibre per millilitres per year
FVC:	Forced vital capacity
GLI:	Global Lung Initiative
HIV:	Human Immunodeficiency Virus
ILO:	International Labour Organisation
SMR:	Standardised mortality rates
SOMP:	Specialist Occupational Medicine Panel
SRR:	Standardised rate ratio
TB:	Tuberculosis

2. ABSTRACT

Background: There is a well-established causal link between asbestos exposure and a spectrum of respiratory, cardiovascular and gastroenterological disease. Higher mortality and morbidity rates are therefore expected in former asbestos miners compared to the general population. Internationally, research in the field has focused on predictors of mortality and mortality rates associated with asbestos-related disease in asbestos-exposed workers.[1-6] Locally, there are no large-scale, long-term published epidemiological studies investigating the mortality rate, the predictors of mortality or mortality trends in this subgroup of South African miners. Therefore, little is known about their overall mortality experience. The true burden of asbestos-related lung disease in former South African miners remains largely unknown.

Aim: This study aims to determine if a former asbestos-exposed cohort of South African miners captured on the Asbestos and Kgalagadi Relief Trusts have a higher mortality rate compared to the general population, to identify the demographic, occupational and medical predictors associated with mortality; and to establish mortality trends in this cohort after leaving the employ of the mines.

Methods: A retrospective cohort mortality study will be conducted on former South African asbestos miners whose demographic, occupational and clinical data were recorded on the Asbestos and Kgalagadi Relief Trusts' Inyosi database. The study will cover the period from 21 March 2004 to 21 March 2023. Vital status data will be obtained on the cohort of miners. Age-, sex-, and calendar year-adjusted standardised mortality rates (SMR) and 95% confidence intervals will be reported, using reference values for the general South African population obtained from the Actuarial Society of South Africa 2008 full model (ASSA2008). This will allow for the objective quantification and comparison of mortality rates in the asbestos miners with that of the general population. Demographic, occupational and clinical determinants of time-to-mortality will be modelled using Cox Regression Analysis. Trends in mortality will be established by examining the all-cause crude mortality rate for each year of the study and by time after cessation of employment.

Conclusion: This retrospective mortality study on former asbestos miners in South Africa aims to objectively quantify the postulated excess mortality rates in former asbestos miners compared to the general population. Furthermore, it seeks to identify significant demographic, occupational and clinical predictors of time-to-mortality in this cohort, in addition to mortality trends since leaving asbestos employment. This information would provide evidence that could enhance existing medical surveillance programmes and inform the health service needs of this subpopulation of South African miners with planned, targeted systemic interventions. Furthermore, the findings could contribute to the

ongoing motivation and justification of adequate compensation for former asbestos miners who develop asbestos-related pulmonary or other systemic diseases.

Keywords: asbestos-related disease, mortality rates, asbestos miners, predictors, risk factors, determinants

3. INTRODUCTION

3.1. Background

Asbestos is a naturally occurring silicate fibre that is suitable for a range of industrial applications by virtue of its physical and chemical properties. South Africa produced approximately 97% of crocidolite, 100% of amosite and was the fifth largest global producer of chrysotile asbestos during the 1970s.[7] Asbestos mining in South Africa was a thriving industry which peaked during the late 1970s.[7] With mounting epidemiological evidence reflecting the toxicity and carcinogenicity of asbestos fibres, considerable efforts were made to reduce the occupational exposure to asbestos post-1970. Classified as a Class 1 carcinogen by the International Agency for Research on Cancer classification (IARC),[8] the new use, mining and production of asbestos products were officially banned in South Africa on the 28 August 2002. The implemented ban, however, did not include pre-existing asbestos-containing materials, such as those encountered during roof repair and replacement. Occupational and environmental exposure to asbestos thus continues.

The causal association between asbestos exposure and a range of pulmonary and non-pulmonary diseases including asbestosis, pleural disease, lung cancer, mesothelioma and cancers of the larynx, ovary and gastrointestinal tract, is well established.[1-6, 9-15] Higher morbidity and mortality rates are thus anticipated in former asbestos miners than in the general population. Moreover, the long latency period and the lack of a clearly defined threshold exposure dose means that ongoing medical surveillance in former asbestos miners remains pertinent even though new use of asbestos was banned more than two decades ago. In recognition of the enduring health risks associated with mining exposures, South African legislation as mandated by the Occupational Diseases and Mine Works Act (ODMWA) entitles former miners to a post-employment biennial benefit medical examination (BME) at an accredited medical facility.[16] The BME is aimed at identifying compensable occupational lung disease and specifically targets former South African miners who have not reached maximum compensation. In March 2003, the Asbestos and Kgalagadi Relief Trusts (“the Trusts”) were established to redress the financial and socioeconomic burdens suffered by former asbestos miners. The Trusts provide a comprehensive suite of services encompassing both financial recompense for qualifying asbestos-related disease and palliative care interventions. Funded by asbestos mining companies which previously operated in South Africa, the

Trusts aim to mitigate the socioeconomic burdens associated with asbestos-related illnesses and improve the quality of life for affected individuals.[17]

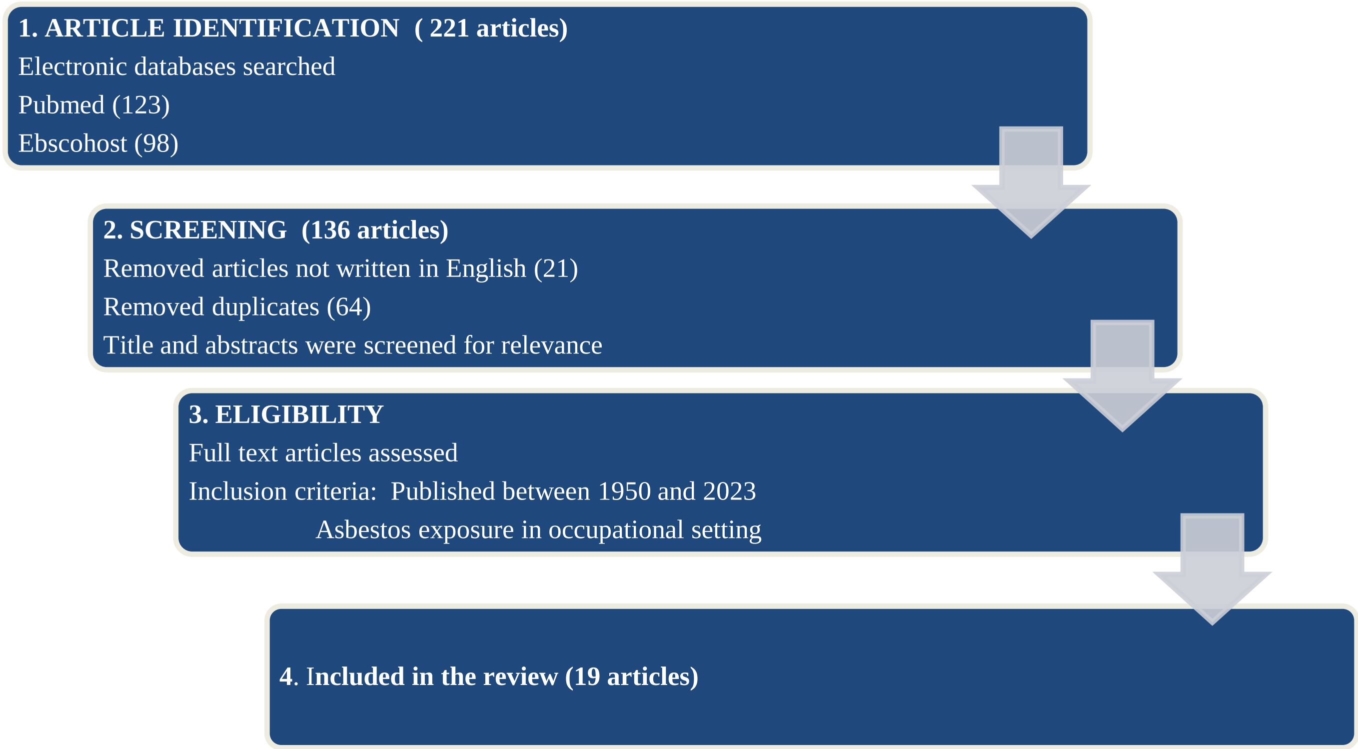
Local and international studies have consistently shown that asbestos-related pulmonary and systemic diseases remain underdiagnosed, untreated and uncompensated.[18-20] This reflects the inadequacy of current medical surveillance programmes and the compensation system. Consequently, former asbestos miners endure health and financial burdens, leaving them far removed from a share of the wealth they laboured to create.

Numerous international studies have documented higher all-cause and cause-specific standardised mortality ratios (SMRs) among asbestos-exposed workers, including miners.[1-6, 9-15] In contrast, research from South Africa, a nation with a thriving asbestos mining industry throughout the 1970s,[7] has produced limited data regarding the overall mortality patterns within exposed worker cohorts. Consequently, the true impact of asbestos-related morbidity and mortality in this population remains largely unquantified.

This study has three aims: (a) to quantify the all-cause SMR in former asbestos miners captured on the Asbestos Relief and Kgalagadi Trusts' database; (b) to identify the demographic, occupational and clinical predictors of mortality in this cohort; and (c) to outline mortality trends demonstrated since exit from asbestos mining employment. The quantitative data generated by this study could inform and enhance the medical surveillance of former asbestos miners and motivate for adequate compensation for asbestosis-related disease.

3.2. Literature Search Strategy

The review included epidemiological mortality studies of former asbestos miners that were published in English from 1950 to 2024. The literature search followed the PICO framework to systematically search for relevant articles in the PubMed, EBSCOHost (Medline/ Africa-Wide Information) and Scopus databases using specific search terms as well as identifying relevant articles cited in the references of the articles identified through the search. The following search terms were used: "mortality" OR "death" AND "asbestos miners" AND "predictors" OR "risk factors" OR "determinants". After the removal of duplicates, articles outside of the specified period and articles not available in English, the title and abstract of the articles were reviewed for relevance. The literature review finally included 19 epidemiological studies of mortality rates and/or their determinants asbestos in former miners.



<u>FIGURE 1</u>: Flow diagram outlining the literature search strategy

3.3. Literature Review

3.3.1. Excess Mortality in Former Asbestos-exposed Workers

<u>Excess all-cause and asbestos-related pulmonary disease mortality rates</u>

Higher morbidity and mortality rates are anticipated in former asbestos miners compared to the general population as result of the causal association between asbestos exposure and a range of pulmonary and extra-pulmonary diseases.[1-6, 9-13] Pulmonary pathologies are characterised by extended latency periods and include parenchymal asbestosis, benign pleural disease, mesothelioma and lung carcinoma. Additionally, asbestos exposure has been implicated in the pathogenesis in some proportion of epithelial malignancies of the larynx, ovary, and gastrointestinal tract. Numerous studies have reported excess SMRs for pulmonary malignancies, particularly for mesothelioma, confirming the carcinogenicity of asbestos fibres.[1-6, 9-15] However, the excess mortality is not limited to malignant pulmonary diseases. Excess all-cause mortality is widely reported, in addition to excess cause-specific mortality associated with non-malignant pulmonary diseases (including parenchymal asbestosis and its associated cardio-pulmonary complications) and malignant extra-pulmonary disease.[1-6, 9-15]

Early studies by Musk *et al*. (2009) and Wang *et al* (2013) examining mortality amongst crocidolite-exposed miners in Wittenoom, Australia and chrysotile-exposed miners in China respectively, found significantly increased SMRs for all-cause mortality and asbestos-related pulmonary disease. Musk *et al* reported a statistically significantly increased SMR for pneumoconiosis (SMR=15.5), lung cancer (SMR

= 1.52), respiratory diseases (SMR = 1.58) and ill-defined diseases (SMR=2.00)[3]; while Wang *et al*. reported a statistically significant increased SMR for all-cause mortality (SMR=1.46), parenchymal asbestosis (SMR=9.62), lung cancer (SMR=1.52) and pulmonary-related cardiac disease (SMR=2.70).[9]

More recently, in an updated Italian cohort study examining mortality amongst chrysotile-exposed miners, Ferrante *et al* (2020) reported a significant increased SMR for all-cause mortality (SMR=1.28; 95% CI: [1.17-1.40]), parenchymal asbestosis (SMR=375.06; 95% CI: [262.68-519.23]) and mesothelioma (SMR=4.30; 95% CI: [1.58-9.37])[1]. Similarly, an Italian study by Pira *et al* (2017) reported an increased SMR for all-cause mortality (SMR=1.35; 95% CI: [1.25 to 1.45]) and mesothelioma (SMR=5.54; (95% CI: [2.22 to 11.4]) in asbestos-exposed miners.[2]

While numerous studies demonstrate excess mortality due to lung cancer, [3-5] both Ferranti *et al* and Pira *et al* interestingly reported increased SMRs for lung cancer which did not reach statistical significance (SMR = 1.14; 95% CI: [0.81-1.55] and SMR=1.16; 95% CI: [0.87-1.52] respectively). Ferrante *et al.* postulate that the results were potentially confounded by smoking, suggesting that smoking was less common among this cohort of Italian miners compared to the general population which accounted for the lower-than-expected SMR.[1] This reasoning remains speculative as no smoking data were available for this cohort.

<u>Excess mortality due to extra-pulmonary asbestos-related disease</u>

In addition to pulmonary-related diseases, studies have reported increased mortality due to laryngeal, ovarian and gastrointestinal malignancies in asbestos-exposed workers.[9-15] A Brazilian study by Saito *et al.* (2022) indicated that the mortality rate for ovarian cancer in municipalities with a history of asbestos mining and cement production exceeded that of the general population (SRR= 1.34).[11] Lin *et al.* (2014) investigated mortality from digestive cancers in a Chinese asbestos miner cohort and reported a SMR of 1.45 (95% CI:[1.10 to 1.90]) for digestive cancers with a clear exposure-response relationship between asbestos exposure and mortality from stomach cancer (SMR=2.39; 95% CI: [1.02 to 5.60]).[12] An Italian study by Piolatto *et al.* (1990) examining chrysotile-exposed miners in Balangero reported an increased SMR for laryngeal cancer (SMR=2.67).[5]

<u>Conclusion</u>

Overall, studies concur that among asbestos-exposed workers all-cause mortality is higher than that of the general population. Furthermore, asbestos-related pulmonary diseases including parenchymal asbestosis with its associated cardiovascular complications, mesothelioma and lung cancer are the principal causes of asbestos-related mortality. Less frequently studied, but also contributing to the mortality burden, are extra-pulmonary malignancies such as those of the larynx, gastrointestinal tract (peritoneal mesotheliomas and gastric cancer), and ovary. The highest SMRs were reported for parenchymal asbestosis and its cardiovascular complications.[3, 6, 9]

South African context

Research on asbestos-exposed miners in South Africa appears to concentrate on mesothelioma mortality trends, compensation processes, and environmental asbestos exposure.[21-23] Notably absent are large-scale, long-term epidemiological studies investigating the mortality experience of this specific subpopulation within South Africa. The overall mortality experience and the true burden of asbestos-related lung disease of former South African miners thus remain largely unknown.

3.3.2. Predictors of mortality in asbestos miners

Socio-demographic predictors of asbestosis-related mortality

Age at first exposure, biological sex, calendar year of employment

Early research evaluating the association between asbestos-related mortality and the age at first exposure revealed conflicting findings.[24] More recent studies indicate that older age at first exposure to asbestos, biological sex and earlier calendar year on entry into asbestos employment are associated with asbestos-related mortality.[11,25-28] In examining the association between temporal patterns of asbestos exposure and asbestos-related mortality in Italian textile workers, Farioli *et al* (2018) reported the highest hazard ratio (HR) in participants aged 35 years or older at first exposure (HR=2.7; 95% CI:[1.1 to 6.4]), a higher HR among males compared to females only when the temporal pattern of exposure was not adjusted for (adjusted HR=1.2; 95% CI: [0.7 to 2.2]) and a significantly lower HR for workers employed after 1968 (HR=0.3; 95% CI: [0.1 to 0.8]).[25] Similarly, a Brazilian study by Saito *et al* (2022) demonstrated higher mortality rates among men for non-malignant asbestos-related disease (SRR in men=2.56; 95% CI:[2.27-2.88]) versus SRR in women=1.19; 95% CI:[0.99-1.43])) and lung cancer (SRR in men=1.33; 95% CI:[1.31- 1.34] versus SRR in women=1.19; 95% CI:[1.17-1.20]).[11] In addition, the authors reported a decrease in the Standard Rate Ratio (SRR) in males post-1970 (pre-1970 SRR=3.26; 95% CI:[2.86-3.70] versus SRR post-1970=1.30; 95% CI:[0.99-1.67]).[11] However, a different pattern was observed in women. The SRR increased in women post-1970 (SRR post-1970=1.35; 95% CI: [1.01-1.79]) compared to SRR pre-1970=1.10; 95% CI: [0.87-1.38]).

In summary, recent studies report higher mortality rates among workers who were older at first exposure, among men compared to women, and among men and women in the pre-1970 era when occupational asbestos exposures were particularly high. Post-1970, considerable efforts were made to reduce occupational asbestos exposure worldwide. The increase in the female mortality post-1970 in the Brazilian study was attributed to environmental and/or domestic asbestos exposure which was associated with a higher prevalence of mesothelioma amongst women. The association between environmental asbestos exposure and higher rates of mesothelioma among females is supported by other studies.[24, 27, 29]

Smoking and asbestos exposure

Both smoking and asbestos exposure are independent risk factors for lung cancer.[8] However, the interaction between the two risk factors in lung cancer, mesothelioma and parenchymal asbestosis causation has been the subject of numerous studies. While consensus among researchers is that an interaction exists, the nature of the interaction is somewhat disputed. A recent study by Klebe *et al* (2020) suggests a multiplicative synergistic interaction between smoking and asbestos exposure in lung cancer causation[30], a finding supported by Wang *et al* (2013) and (2014).[9,10] Contrastingly, El Zoghbi *et al* (2017), Ngamwong *et al* (2015) and Liddel (2001) assert that the interaction is additive.[31-33] Markowitz *et al* (2013) demonstrated that the joint effect of smoking and asbestos exposure was additive for lung cancer (rate ratio=14.4; 95% CI:[10.7–19.4]) but multiplicative for asbestosis (rate ratio=36.8; 95% CI: [30.1–45.0]) among a cohort of asbestos-exposed insulators in North America.[34] The synergistic interaction between smoking and asbestos exposure on asbestosis causation was supported by Ferrante *et al* (2020). Berry *et al* (1985) reported that there was no evidence to suggest that smoking combined with asbestos exposure increases the risk of mesothelioma.[35]

Pathophysiologically, cigarette smoking increases the permeability of the lungs which facilitates the penetration of asbestos fibres into the lung parenchyma. Furthermore, research suggests that there is greater retention of asbestos fibres in the lungs of smokers compared to non-smokers.[36] Smoking also dysregulates mucociliary function, diminishing the ability to clear foreign material, such as asbestos, from the airways.[37] When considering these factors, the occurrence of increased asbestos–related malignant and non-malignant pulmonary disease in individuals dually exposed to cigarette smoke and asbestos is biologically plausible.

Current evidence therefore suggests that smoking in asbestos-exposed workers increases the risk of lung cancer and parenchymal asbestosis, with no increased risk for mesothelioma demonstrated. While the interaction between smoking and asbestosis is multiplicative, the nature of the interaction between smoking and asbestos exposure on lung cancer causation remains uncertain. More recent studies support a multiplicative effect[30] while earlier studies supported an additive effect.[31-33] Further empirical epidemiological studies are needed given the conflicting results.

Tuberculosis and asbestosis exposure

While the association between silicosis and tuberculosis (TB) is well-recognised,[38, 39] the association between asbestosis and TB is less clear. Few studies have examined this association. The findings of existing studies appear to be at odds with each other.[40, 41] Segarra-Obiol *et al* (1983) did not reveal a statistically significant difference in the incidence of TB in patients with asbestosis (3.87%); in asbestos-exposed workers with no evidence of asbestosis (3.45%) and healthy individuals (3.93%). The authors therefore concluded that asbestosis was not a risk factor for TB.[40] A later cohort study by Tse *et al* (2012) examined the prevalence of pulmonary TB in workers with asbestosis in Hong Kong. A high prevalence of TB was reported (36.29%). The authors postulated that decreased immune responsiveness increased susceptibility to TB in this cohort.[41] Given the paucity in research and conflicting findings, the association between TB and asbestos-related morbidity and mortality remains unclear.

HIV status and asbestos-related mortality

The increased risk of cancer in individuals living with HIV/AIDS is well-established.[42-44] Literature investigating the association between HIV/AIDS and asbestos-related mortality is scarce. The nature of the association is therefore unknown. A case study by James *et al* (2009) describes mesothelioma diagnosed in a HIV positive, asthmatic male with a positive cigarette smoking history, who had a relatively short six-month history of asbestos exposure. The authors theorise that the immunosuppression present in HIV/AIDS patients enhanced the patient's susceptibility to mesothelioma.[45] This finding suggests that HIV/AIDS could be a risk factor for mesothelioma independent of significant asbestos exposure. The potential interactive effect of HIV/AIDS in asbestos-exposed individuals on the risk of asbestos-related mortality and morbidity needs further study.

Comorbidities and asbestos-related disease

Chronic Obstructive Pulmonary Disease (COPD), asbestos exposure and mortality

Although limited in number, studies have investigated the association between asbestos exposure and COPD. [46-48] Moitra *et al* (2020) reported an increased prevalence of COPD with asbestos exposure (PR=1.44; 95% CI:[1.01-2.05]) in insulators from Alberta, Canada.[46] An earlier study by Bergdahl *et al* (2004) showed increased mortality from COPD due to occupational dust exposure including asbestos fibre dust (hazard ratio (HR)=1.10; 95% CI:[1.06–1.1]).[47] While it is biologically plausible that the aberrant physiological functioning observed in individuals with COPD increases their susceptibility to asbestos-related morbidity and mortality, studies investigating this association are limited. The asbestos-related mortality rate in individuals with COPD who are exposed to asbestos has not been quantified.

Conclusion

Research indicates that age at first exposure to asbestos, biological sex, calendar year of entry into asbestos employment, smoking, HIV/AIDs and COPD are potentially associated with asbestos-related mortality.

Occupational predictors of asbestosis-related mortality

Occupational factors and their association with asbestos-related mortality and morbidity are well-established; the carcinogenic association having been extensively studied. There is consensus among researchers that cumulative asbestos exposure, duration of exposure and asbestos fibre dimension and type are associated with asbestos-related morbidity and mortality.[49-63] Asbestos exposure levels in the mining sector vary with respect to job category and the underground or surface nature of work. The nature of mine work can thus affect the cumulative exposure and by extension the risk of asbestos-related morbidity and mortality.

Cumulative asbestos exposure, dose-response relationships and duration of exposure

The International Agency for Research on Cancer (IARC, 1987) recognises asbestos as a Group I carcinogen causally associated with mesothelioma and lung cancer. The carcinogenic risk is primarily related to the duration of exposure and cumulative exposure dose.[49] Numerous studies have corroborated this association.[50-55] In a study investigating the relationship between cumulative asbestos exposure and asbestos-related mortality in Italian cohorts of long-term chrysotile- and amphibole-exposed workers, Luberto *et al* (2019) reported an increasing trend in all-cause and cause-specific mortality per tertile of cumulative exposure in both sexes. The SMR was increased for parenchymal asbestosis (SMR: men=507; 95% CI:[455,3-563.4] and women=1023; 95% CI:[761.9-1345.5]), pleural malignancies (SMR: men=22.3; 95% CI: [19.9-25.0] and women=48.10; 95% CI:[38.6-59.1]), peritoneal malignancies (SMR: men=14.1; 95% CI: [11.5-17.2] and women=15.1; 95% CI: [10.2-21.5]) and lung malignancies (SMR=1.67 in both men and women).[50] These findings were supported by Ferrante *et al* (2020) who reported increased SMRs for mesothelioma, lung cancer and asbestosis with increasing cumulative asbestos exposure. When quantifying the cumulative dose associated with asbestos-related morbidity and mortality in chrysotile-exposed miners in China, Wang *et al* (2013) indicated that significantly increased mortality from lung cancer was observed in smokers at levels of 20 fibre/ml-years or more, and in non-smokers at levels of100 fibre/ml-years.[9] No excess lung cancer mortality was observed in cumulative exposures less than 20 fibre/ml-year.[9] A similar trend was demonstrated parenchymal asbestosis.[9] In their study, Ferrante et al (2020) reported no deaths from parenchymal asbestosis when cumulative exposures were below 27 fibre/ml-year. However, the risk of mortality from parenchymal asbestosis increased with higher exposures. This finding supports an earlier study by Tossavainen *et al* (1997) which suggests that asbestosis usually becomes apparent at cumulative exposure levels of 25 fibre/ml-year. The accurate approximation of a threshold cumulative exposure dose is challenging but numerous studies concur that clinical asbestosis might be induced by exposures as low as 2–5 fibre/ml-years.[64-66] Furthermore, asbestos-related diseases usually become apparent clinically at cumulative doses of 20-25 fibre/ml-year.[1,9,62] At these levels of exposure, the incidence of asbestos-related disease and the associated mortality rises sharply.[1] No increased risk for lung cancer or mesothelioma was observed at asbestos exposure levels < 0.1 fibre/ml-years.[9]

Farioli *et al* (2018) observed an increased hazard ratio (HR) of asbestosis mortality with exposure duration (HR=2.4 for ≥15 years compared with <5 years, P trend = 0.014).[25] Similar findings were reported by Wang *et al* (2013) who demonstrated a 3.5-fold increase in lung cancer with more than 10 years duration of employment and a 5.3-fold increase with more than 20 years duration of employment compared to less than 10 years duration.[9] A similar trend was observed for non-malignant pulmonary disease. Farioli *et al* (2018) further indicated that other time-related factors such as latency (from first exposure), the calendar year of first exposure and the time since last exposure must be considered when assessing the effects of employment duration.[25] The authors reported a decrease in the HR for employment duration from 8.5 to 3.2 after adjustment for year of first exposure, time since last exposure and biological sex. The observed attenuation in the hazard ratio (HR) for employment duration and asbestosis following adjustment for year of first exposure, time since last exposure, and biological sex suggests potential confounding by these variables. The unadjusted HR likely reflects an association that is partially attributable to these factors.

The risk of asbestosis is likely to correlate more closely with cumulative asbestos exposure (rather than duration of employment), which is a product of both exposure intensity and duration. Historically, asbestos exposure intensity was demonstrably higher in the pre-1970 era. Consequently, individuals commencing employment earlier may have received a higher cumulative dose compared to those entering the workforce later, even if their total employment durations were similar.

Asbestos fibre dimensions and type

While the carcinogenicity of all asbestos types is recognised by the IARC, considerable variation in the risk of asbestos-related disease across industries has been observed. This difference can be attributed to varying fibre loads, dimensions and types.[54-64] Research indicates that long, thin fibres especially those greater than 10 μm may have greater carcinogenic potential than shorter, wider fibres.[54-60] Longer fibres are less easily cleared and therefore retained within the lung parenchyma for longer periods. Lippmann *et al* (1988) postulated that fibre dimension and load influence the development of specific asbestos-related diseases. They concluded that parenchymal asbestosis was related to the surface area of retained fibres; mesothelioma was associated with the number of fibres longer than 5 microns and thinner than 0.1 microns and that lung cancer was associated with fibres longer than 10 microns and thicker than 0.15 microns.[60] Furthermore, studies suggest that the carcinogenic potential across fibre types are differential.[54,63] In quantifying the risks of mesothelioma and lung cancer in relation to the type of asbestos exposure in occupational cohorts, Hodgson *et al* (2000) reported that the risk of mesothelioma from chrysotile, amosite and crocidolite asbestos was in a ratio of approximately 1:100:500 respectively and that the risk differential between chrysotile and amphibole fibres (amosite and crocidolite) for lung cancer is between 1:10 and 1:50.[54] Studies therefore suggest that asbestos fibre load, dimension and type are important determinants of asbestos morbidity and mortality.

<u>Nature of occupational exposure and job category</u>

Asbestos exposure varies with job category and the underground or surface nature of occupational exposure.[67, 68] In analysing asbestos exposure of Italian chrysotile miners and millers Silvestri *et al* (2020) demonstrated varying exposure levels by job category. Asbestos concentrations in milling areas incorporating crushing, mixing and packaging ranged from 50 to up to 250 fibre/ml with beneficiation demonstrating the highest exposure level.[67] Similarly, Mutetwa *et al* (2022) indicated that higher prevalence of asbestos-related diseases may be related to specific job tasks in the cement manufacturing industry due to different levels on cumulative exposure.[68]

<u>Conclusion</u>

There is consensus among researchers that the principal occupational predictors of asbestos-related mortality include cumulative asbestos exposure, duration of exposure, asbestos fibre dimension and type, job category and the underground or surface nature of work. To our knowledge, no South African studies have been conducted to investigate the association between occupational risk factors and asbestos-related mortality.

Clinical predictors of asbestosis-related mortality

The long latency period between asbestos exposure and the onset of disease is well-described and is estimated at 20-50 years.[69] Asbestos-related disease is therefore typically characterised by slow clinical progression,[70, 71] rendering it amenable to longitudinal study. Despite this, relatively few studies both globally and locally have investigated the association between abnormal clinical parameters observed in asbestos-exposed workers over time and the empirical prediction of subsequent asbestos-related death.[72] Consequently, relatively little is known about the way in which symptoms, abnormal physical examination findings, decreased lung function and radiological abnormalities quantitatively predict the risk of mortality in asbestos-exposed workers.

Radiological and lung function abnormalities predicting asbestos-related mortality

Clinical studies analysing trends in disease progression have been descriptive, rather than predictive. Studies have focused on the prevalence of radiological and lung function abnormalities, in addition to longitudinal changes in radiological patterns and lung function observed in workers with long-term occupational asbestos exposure.[73-80] In a study evaluating temporal changes in the pattern and extent of parenchymal abnormalities in previously asbestos-exposed workers, Silva *et al* (2015) demonstrated an increased extent of parenchymal abnormalities in 81% of participants at three to five years follow up, following the cessation of asbestos exposure.[73] Algranti *et al* (2013) and Moshammer *et al* (2008) showed decreasing lung function in asbestos-exposed workers over time.[81, 82] The decreasing trend in lung function was influenced by cumulative asbestos exposure, smoking history and radiological abnormalities, with the combined effects of smoking and asbestos exposure accelerating lung function decline. A study by Miller *et al* (2018) investigated the correlation between radiological and lung function parameters.[83] The authors reported a significant association between radiological changes and pulmonary function findings among amphibole-exposed miners in Libby, Montana. Pleural thickening and parenchymal abnormalities were both associated with significantly lower forced vital capacity and diffusion capacity values, more so with parenchymal abnormalities.

However, these descriptive clinical studies have not related the abnormal clinical parameters to the quantitative prediction of mortality risk from asbestos-related disease. Studies aimed at establishing definitive links between abnormal clinical parameters and the prediction of mortality risk are scarce, and to our knowledge non-existent in the South African mining population. Markowitz *et al* (1997) examined the way in which abnormal clinical parameters (physical examination, radiological and spirometry findings) predicted asbestos-related mortality in a North American cohort of insulators. The authors reported a dramatic increase in the 10-year risk of death due to asbestosis with increasing radiographic profusion category identified on the baseline chest X-ray. The 10-year risk of death rate increased from 0.9% to 2.4%, 10.8%, and 35.4% for ILO profusion categories 0, 1, 2, and 3, respectively, indicating that the profusion of parenchymal abnormalities significantly predicted mortality risk.[72] Furthermore, the authors reported that the presence of abnormal clinical findings which included dyspnoea, a low forced vital capacity, and/or physical examination findings typical of parenchymal asbestosis (crackles, clubbing, or cyanosis) increased the risk of subsequent death from asbestosis 2- to 6-fold.[72]

The prognostic value of radiological findings in the prediction of asbestosis-related mortality as indicated by Markowitz *et al*, was supported by Vehmas and Oksa (2014) and an earlier study by Liddell and MacDonald (1980).[72, 84, 85]

Conclusion

In summary, few international and local studies have evaluated the positive predictive value of abnormal radiological and lung function findings with respect to asbestos-related risk of mortality. Despite the limited number and lack of studies conducted in mining populations, radiographic and lung function abnormalities have been shown to quantitatively predict the risk of asbestos-related mortality.[72] Further investigation into the prognostic value of these clinical parameters in the mining population is thus warranted. Objective data concerning the prediction of mortality risk could motivate for evidence-based medical surveillance programmes and support for appropriate compensation programmes. This could potentially mitigate the morbidity, mortality and financial burdens associated with asbestos-related mortality.

3.3.3 Mortality trends

To date few studies have examined the mortality trends in asbestos miners since leaving the employ of mines. As a result of latency, the risk of asbestos-related morbidity and mortality remains even after exposure has ceased. Furthermore, the loss of access to medical care once workers have left the mines could contribute further to the health and financial burdens in this subpopulation of miners.

In their Italian cohort, Ferrante *et al* (2020) reported high all-cause and cause-specific mortality rates within the first year of leaving the employ of the mines. The authors demonstrated an all-cause SMR of 1.98 (95% CI: [0.86-3.91]), a SMR of 1018.85 (95% CI: [25.47-5677.02]) for asbestosis and a SMR of 89.38 (95% CI: [2.23-498.02]) for mesothelioma within the first year of leaving the employ of the mines. The mortality rates decreased with time but remained significant even after 10 years.[1] This finding suggests that miners probably left the employ of the mines due to ill health. However, it underscores the effect of latency and the conclusion that asbestos-related mortality remains significant for many years even after exposure has ceased. Objective data quantifying the persistent risk of asbestos-related mortality despite the cessation of exposure are crucial. It can serve to inform medical surveillance programmes, motivate for adequate compensation and allocation of public health resources.

3.4 Knowledge gap and motivation for the study

There are no large-scale, long-term published epidemiological studies investigating the mortality rate, the predictors of mortality or mortality trends in former South African asbestos miners. Therefore, little is known about the overall mortality experience and the true burden of asbestos-related lung disease in this cohort of miners.

The need for ongoing medical surveillance of former asbestos miners remains pertinent, given the long latency period and the lack of a clearly defined exposure threshold. The identification of demographic, occupational and health predictors of mortality and the delineation of mortality trends after exiting asbestos mining employment could potentially inform and enhance the current medical surveillance of former asbestos miners. Furthermore, the quantitative data generated by the study could provide evidence-based motivation for adequate compensation and the allocation of public health resources.

This research study aims to evaluate the overall mortality rate and its predictors within a cohort of asbestos-exposed miners recorded on the Asbestos Relief and Kgalagadi Trusts' Inyosi database between 21 March 2004 and 21 March 2023. To our knowledge, this will be the first study of its kind in South Africa. This large-scale, long-term epidemiological study has the added benefit of variable periods of employment and cumulative exposures among miners, allowing for the comparison between short- and long-term asbestos exposure and the effect of cumulative exposure on mortality rates. Furthermore, it will assess the ability of longitudinal changes in clinical parameters to quantitatively predict asbestos-related mortality.

The novel information generated by the study will be instrumental in informing the development and implementation of improved public health measures pertaining to former asbestos miners. Specifically, the study findings hold the potential to optimise medical surveillance programs through the identification of high-risk groups and more frequent monitoring, leading to earlier detection of asbestos-related pathologies. This approach could facilitate earlier detection of lung cancer cases, thereby expanding therapeutic options and potentially reducing lung cancer mortality. Early identification of benign asbestos-related diseases, such as parenchymal asbestosis, would enable timely intervention, potentially mitigating complications. Such interventions may ameliorate symptoms, preserve pulmonary function, and enhance overall quality of life within this cohort. Consequently, early intervention strategies could potentially reduce the economic burden on public health resources. The quantitative data generated by this study can facilitate efforts aimed at securing greater compensation for this vulnerable subpopulation of miners. In addition, research findings could encourage the families of deceased asbestos miners to exercise the statutory autopsy right to secure compensation for family members posthumously.

Ultimately, this research holds the potential to identify the long-term health needs of this susceptible population of miners and improve the overall well-being within this cohort.

3.5 Research Questions

- Are former asbestos miners from South Africa at increased risk of excess mortality compared to the general population?
- Which demographic, occupational and medical predictors are significantly associated with the excess mortality of former asbestos miners?
- What are the mortality trends in this cohort of former miners following their exit from employment?

3.6 Hypothesis

It is hypothesised that former asbestos miners have a higher mortality rate than the comparable general population. It is further hypothesised that demographic, occupational and clinical predictors are significantly associated with time-to-mortality in this subpopulation of miners. Demographic predictors hypothesised to be significantly associated with mortality in this cohort include age on entry into the workforce and biological sex; occupational predictors include the duration of asbestos exposure, type of exposure, and job category, while clinical predictors include radiological and/or lung function impairment. An increased cumulative mortality after exit from asbestos mining employment is expected, given the long latency period between asbestos exposure and the onset of asbestos-related symptoms and disease. However, the annual mortality rate may show a different pattern as demonstrated in a mortality study of gold miners by Bloch *et al* (2018).[86]

3.7 Aim and Objectives

The aims and objectives of this study are:

1. To describe the demographic, occupational and clinical characteristics of a cohort of former asbestos miners in South Africa on entry into a database established by the Asbestos and Kgalagadi Relief Trusts.
2. To determine the annual crude mortality rate and standardised mortality ratio (SMR) in this cohort for period 21 March 2004 to 21 March 2023. The SMR will determine if former asbestos miners have a higher mortality ratio than that of the general population.

3. To identify socio-demographic, occupational and clinical predictors associated with time-to-mortality in this cohort through Cox Regression Analysis
4. To investigate trends in mortality in this cohort of asbestos miners by examining the annual crude mortality rate by calendar year for the period of the study

4. METHODOLOGY

4.1. Study Design

A retrospective cohort mortality study will be conducted on former South African asbestos miners whose socio-demographic, occupational and clinical data were captured on the Trusts' Inyosi database. This study design approach offers several advantages. Leveraging existing, objectively measured data from the Trusts' Inyosi database minimises the time and resource expenditure associated with data collection. Quality control measures implemented on the database mitigate potential biases inherent in data collection. The large sample size and extended follow-up period within the cohort translate to significant statistical power, allowing for robust analysis.

The study will utilise the existing data to calculate the SMR. This metric, expressed as the ratio of observed deaths in the cohort to expected deaths based on the general South African population, permits the comparison of mortality patterns between former asbestos miners and the general population.

Furthermore, a Cox Proportional Hazards Regression analysis will be conducted to identify factors significantly associated with time-to-mortality within the cohort. The results of this analysis will be reported as hazard ratios (HRs), adjusted for potential confounding covariates. These adjusted hazard ratios (aHRs) will quantify the instantaneous risk of mortality associated with each significant predictor.

Mortality trends will be explored through the computation of crude mortality rates for each year of the study period and by year of exit from asbestos employment. This will elucidate potential temporal variations in mortality risk attributable to predictors.

4.2. Data Source

This retrospective cohort study will utilise pre-existing data from the Trusts' Inyosi database. This repository encompasses a population of former asbestos miners who have ceased employment within the South African mining industry. Most of this population were crocidolite exposed with minorities exposed to amosite and chrysotile asbestos fibres. The data encompasses the period from 2004 till present and captures:

1. Demographic data and smoking history
2. Occupational data, i.e. the type of asbestos exposure, duration of service, mine location, the exit date from mine employment
3. Clinical data abstracted from medical examinations performed by medical officers employed by the Trusts. Clinical data included past medical history, occupational history and physical examination findings. Furthermore, a specialised occupational medicine panel (SOMP) reported and classified chest radiograph (CXR) and spirometry findings.

The Trusts obtained informed consent from each participant prior to their entry onto the Inyosi database. This included consent to the use of their data for future research (**Appendix 1**). Furthermore, approval for the utilisation of this data for the present study was granted by the Trusts' Board of Trustees following the submission of a detailed research synopsis by the principal investigator. To ensure adherence to ethical standards, this research proposal will be submitted to the University of Cape Town's Health Research Ethics Committee for ethics approval before study initiation.

4.3. Study Population and Sample Size

The study population will comprise a cohort of former South African asbestos miners captured within the Trusts' Inyosi database during the period 21 March 2004 to 21 March 2023. The database contains demographic, occupational and clinical data on the cohort of miners, in addition to vital status data and the date of death (where applicable). The vital status and date of death of cohort participants were obtained by the Trust for operational purposes through a linkage process facilitated by Xpert Decision Systems (XDS). XDS is an independent third-party linkage specialist able to access the Home Affairs database and provide vital status data for a given South African identity (ID) number.

The Trust submitted 16 127 South African ID numbers on the Inyosi database to XDS who provided Home Affairs vital status output on 21 March 2023 as follows:

Alive	7876
Deceased	7325
Invalid ID number	926
Total	16127

The following exclusion criteria will be applied to increase the study's internal validity:

1. Non-South African asbestos miners will be excluded from the study cohort.
2. Individuals whose ID numbers captured on the Inyosi database do not correspond with those within the Home Affairs database.
3. Individuals who were not exposed to asbestos in an occupational setting.
4. Individuals who died between the date of employment exit and entry on to the Trusts' database.
5. Individuals who died in the interval between their entry on to the database and their initial clinical examination.

The entire sample will be used for analysis following the application of exclusion criteria listed above. This will ensure that the study is adequately powered which will allow for a high level of precision in estimating of the mortality experience of this group of miners.

4.4. Measurement Tools

<u>The Asbestos and Kgalagadi Relief Trust Medical Evaluation Form</u>

At the baseline medical assessment, standardised medical evaluation forms (**Appendix 2**) were used by examining medical officers to capture participant demographic, medical history, occupational history, and clinical data.

Demographic data included age and biological sex; the relevant medical history documented included HIV status and prior tuberculosis (TB) diagnosis; the occupational data recorded included the mine location, job type, and duration of asbestos exposure (entry and exit dates) and the clinical data documented included clinical symptoms (dyspnoea and weight loss) and physical examination findings.

Standardised questions from the form were used to elicit respiratory symptoms, particularly dyspnoea. The questions were aligned with the validated Medical Research Council Criteria (MMRC)[87] and the severity and grade of dyspnoea were documented accordingly.

When available, occupational data were cross-checked with occupational records. Furthermore, pharmacy scripts and outpatient clinic card attendance records from hospitals were used to verify information about past and present illnesses and comorbidities, when available. A geographic mapping system developed by the Trusts medical co-ordinator was employed to confirm the reported mine locations and types of asbestos exposure disclosed by former miners.

The Specialist Occupational Medicine Panel (SOMP) Data Collection form

Following the initial medical assessment, a member of the Specialist Occupational Medicine Panel (SOMP) utilised a standardised form (**Appendix 3**) to summarise the clinical information collected by the examining medical officer and record the radiological and spirometry data for each participant. The SOMP consisted of medical specialists trained in the fields of occupational medicine or radiology. In addition, the SOMP members were trained in reading radiological data in accordance with the International Labour Organisation's (ILO) Classification of Radiographs of Pneumoconioses[88], which standardises the reporting of pneumoconioses findings on chest-X-rays (CXRs).

Data captured on the SOMP form by the SOMP evaluators included the quality of the spirogram and CXR, the quality of the medical examination conducted by the medical officer, the relevant background and occupational history of each participant, the raw spirometry data (FEV_1, FVC and FEV_1/FVC ratio), radiological data including the profusion category, the presence of classifiable pleural abnormalities and other radiological abnormalities as per ILO Classification of Radiographs of Pneumoconioses. Furthermore, the SOMP evaluators were required to formulate a management plan which included a repeat spirogram or CXR where necessary, referral for a BME or a request for a review by another SOMP panel, where indicated.

The SOMP form facilitated the clinical categorisation of participants based on summarised clinical symptoms, examination findings, radiological and spirometry data. This categorisation determined eligibility for compensation.

To increase the accuracy, validity and consistency of radiological reporting, CXRs were evaluated and reported by a team of two independent readers, i.e. a radiologist and an occupational medicine practitioner, both trained and experienced in the use of the ILO Classification of Radiographs of Pneumoconioses. The classification of radiological data was done by consensus between the two readers with a tendency for the radiologist’s reading to prevail. CXR quality was assessed before interpretation. Unreadable or uninterpretable CXRs were referred for repeating. CXR reporting was performed by readers with full knowledge of the participant's medical, occupational, and smoking history. Where the first SOMP panel found the radiological classification of cases to be difficult, a second SOMP panel was enlisted to adjudicate the CXR using the ILO Classification. The more severe classification was taken as final. Pulmonary function was assessed using spirometry following current European Thoracic Society/American Thoracic Society (ERS/ATS) guidelines.[89,90] Spirometers were regularly calibrated, maintained, and serviced to ensure reliable data collection. Models known to produce high-quality spirograms were employed (e.g., Model IQ Tech, Schiller, and Coco). Spirometry results were deemed acceptable only if the spirogram quality was satisfactory. Unacceptable tests were repeated until at least three acceptable efforts were obtained from each participant. Technicians or medical officers performing spirometry were trained in conducting spirometry testing.

The Global Lung Function Initiative-global (GLI) reference equations will be used to categorise lung function impairment to ensure uniformity.[91-93] Raw spirometry data captured on the database will be used to generate z-scores for each parameter including FEV_1, FVC and FEV_1/FVC ratio using a GLI calculator available from the ERS. The lung function will be categorised into obstructive, restrictive and mixed ventilatory defects based on the lower limit of normal of lung function parameters i.e., z-scores < -1.65. Categorisation and subcategorisation of lung function will be based on z-scores as follows:

Lung Function Category	**Reference Values**
Normal lung function	FEV_1/FVC ratio Z-score > -1.64 FEV_1 z-score > -1.64 FVC z-score > -1.64
Obstructive Lung Function	FEV_1/FVC ratio z-score < -1.64 FEV_1 z-score < -1.64 FVC z-score ≥ -1.64
Obstructive Defect Subcategories	
Mild	FEV_1 z-score= -1.64 to -2.0
Moderate	FEV_1 z-score= -2.0 to -2.5
Moderately severe	FEV_1 z-score= -2.5 to -3.0
Severe	FEV_1 z-score= -3.0 to -4.0
Very severe	FEV_1 z-score < -4.0
Restrictive Lung Function	FEV_1/FVC ratio z-score ≥ -1.64 FVC z-score < -1.64 FEV_1 z-score ≥ -1.64
Restrictive Defect Subcategories	
Mild	FVC z-score= -1.64 to -2.0
Moderate	FVC z-score= -2.0 to -2.5
Moderately severe	FVC z-score= -2.5 to -3.0
Severe	FVC z-score= -3.0 to -4.0
Very severe	FVC z-score < -4.0
Lung Function Category	**Reference Values**
Mixed Ventilatory Defect	
Predominantly Obstructive Defect	FEV_1/FVC z-score < -1.64 FVC z-score < -1.64 Greater decrease in FEV_1/FVC z-score compared to FVC z-score
Predominantly Restrictive Defect	FEV_1/FVC ratio z-score >-1.64 FVC z-score < -1.64 Greater decrease in FVC z-score compared to FEV_1/FVC z-score

Appendix 4 (Table 1) details the operationalisation of variables employed in the study. It includes references, cut-offs, and specific guidelines used for the categorisation and subcategorisation of variables. Additionally, Table 1 outlines the quality control measures implemented to ensure data integrity.

4.5. Data Capture and Protection

Data Transcription and Protection

Trained data capturers, overseen by the Trust's medical co-ordinator, systematically abstracted relevant sociodemographic, occupational, and clinical data from the Medical Evaluation and SOMP forms onto an electronic database. To maintain the reliability of the captured data, a standardised electronic data collection instrument (Excel spreadsheet) was utilised and data capturers trained by the Trusts' medical co-ordinator were employed. This ensured data uniformity and minimisation of transcription errors. The electronic database was password-protected with access restricted to the Trusts' medical co-ordinator and authorised personnel. This secure repository safeguarded data integrity and minimised unauthorised access.

The original paper-based health records of the former asbestos miners will be securely stored within a locked filing cabinet at the Trusts' premises for a retention period of 40 years as per statutory requirements. This extended retention period ensures adherence to ethical and legal requirements for data storage.

Vital Status Assessment

The vital status of cohort participants was ascertained through a linkage process facilitated by Xpert Decision Systems (XDS), an independent third-party linkage specialist able to access the Home Affairs database and provide vital status data for a given South African identity (ID) number. Following successful linkage through the South African ID number, the vital status and the date of death was captured on each participant where applicable by XDS. This data was returned to the Trusts' medical coordinator and added to the existing electronic database containing participant data. Due to potential limitations in data quality and completeness, the cause of death reported on the Home Affairs database was not included. As of 21 March 2023, vital status and date of death data were successfully obtained on a total of 15 201 participants (alive=7876; deceased=7325) with invalid ID numbers identified for 926 participants. This data was added to the existing electronic database. For miners with missing follow-up data, the last date on which they were known to be alive will be recorded as the censoring date in survival analysis.

Data Anonymisation

To safeguard participant confidentiality, data on the electronic database will be de-identified by the Trusts' medical co-ordinator using unique identifiers assigned to each participant. Researchers will receive anonymised data in electronic format encompassing sociodemographic, occupational and clinical data, in addition to the vital status data and date of death (where applicable) for the defined study cohort.

5. DATA MANAGEMENT

5.1 Operational Definitions

Appendix 4 (Table 1) details the operationalisation of variables utilised in this study. It defines the criteria used in the clinical categorisation of the former miners i.e., the standardised reference and cut-off values used for the clinical classification of radiological and spirometry data. In addition, it outlines the quality control measures implemented by researchers to ensure standardisation and uniformity during data collection. These measures enable the validity and reliability of the data measurement tool to be critically considered, reinforcing the integrity of the collected data.

5.2 Variables

Variable	Variable Type	Levels of Variables
Outcome Standardised Mortality Rate	Numerical	N/A
Sociodemographic Predictors		
Age at initial examination (years)	Nominal	l5-24.9/ 25-34.9/ 35-44.9/ 45-54.9/ 55-64.9/ ≥ 65 years
Biological sex	Binary	Male/Female
Previous/Current/Recurrent TB	Binary	No/Yes
Smoking	Nominal	Never/ Previous/ Current
Co-morbidities HIV positive Asthma or COPD Diabetes Cardiovascular disease Hypertension Previous chest trauma Other comorbidities	Binary	Absent/Present
Occupational Predictors		

Type of asbestos exposure	Nominal	Crocidolite/Amosite/Chrysotile/Mixed
Occupational category	Nominal	Underground only/Surface only/Both/ Unspecified
Mixed mining exposures	Binary	Asbestos only/Mixed exposures (asbestos + coal/silica)
Mine location	Nominal	Kuruman/Penge/Msauli/Other mines
Age at entry into asbestos employment (years)	Nominal	l5-24.9/ 25-34.9/ 35-44.9/ 45-54.9/ 55-64.9/ ≥ 65 years
Age at exit from asbestos employment (years)	Nominal	l5-24.9/ 25-34.9/ 35-44.9/ 45-54.9/ 55-64.9/ ≥ 65 years
Time in asbestos employment (years)	Ordinal	0-4.9/ 5-9.9/ 10-14.9/ 15-19.9/ 20-24.9/ ≥ 25 years
Calendar year of entry into asbestos employment	Nominal	After 2000/ 1990-1999/ 1980-1989/ 1970-1979/ Before 1970
Calendar year of exit from asbestos employment	Nominal	After 2000/ 1990-1999/ 1980-1989/ 1970-1979/ Before 1970
Time since last exposure	Ordinal	0-4.9/ 5-9.9/ 10-14.9/ 15-19.9/ 20-24.9/ ≥ 25 years
Clinical Predictors		
Symptoms		
Dyspnoea	Ordinal	MMRC Grade I – IV
Physical examination		
Body Mass Index	Nominal	Normal/ Underweight/ Obese/ Overweight
Abnormal physical examination	Binary	Absent/Present
Signs of cardiac failure	Binary	Absent/Present
Radiological		
ILO profusion category	Ordinal	ILO Profusion Category 0-3
Pleural abnormalities	Binary	Absent/Present
Pleural plaques	Binary	Absent/Present
Costophrenic angle obliteration	Binary	Absent/Present
Diffuse pleural thickening	Binary	Absent/Present
Lung cancer	Nominal	Absent/Radiological suspicion/Histological evidence
Mesothelioma	Nominal	Absent/Radiological suspicion/Histological evidence
Other abnormalities (as per ILO)	Binary	Absent/Present
Spirometry		
Spirometry parameters (litres) FEV_1/FVC (%) FEV_1 (litres) FVC (litres)	Numerical	N/A
Spirometry categorisation	Nominal	Normal/Obstructive/Restrictive/Mixed

Subcategorisation of obstructive and restrictive lung defects (see Table 1)	Nominal	Mild/Moderate/Moderately severe/Severe/Very severe
Mixed defects	Nominal	Absent/Predominantly obstructive/Predominantly restrictive

6. STATISTICAL ANALYSIS

6.1 Descriptive Statistics

STATA version 18.0 will be employed for all statistical analyses.[94] Descriptive statistics will be utilised to characterise the distribution of each measured predictor variable. Continuous variables, including age, body mass index (BMI), and duration of employment, will be transformed into categorical variables to facilitate subsequent analyses. Frequencies of categorical data will be expressed as percentages and significant differences in the distribution of categorical variables across vital status groups (e.g., alive vs. deceased) will be assessed with Chi-squared tests. The results will be reported with 95% confidence intervals to provide a measure of statistical precision. Results will be presented in Table 2.

6.2 Mortality Analysis

The number of person-years contributed to the study by each participant will be quantified as the duration between their initial examination date and either their date of death or the censor date for surviving participants i.e. 21 March 2023. The crude mortality rate will be calculated by dividing the observed number of deaths by the total person-years contributed by all participants during the study period. Crude mortality rates will be determined for each category of the predictor variable and presented within the descriptive statistics table (Table 2).

The Standardised Mortality Ratio (SMRs) will be computed by dividing the observed number of deaths by the expected number of deaths per person-years contributed by all participants during the study period. The expected number of deaths within a general South African population sample matched for age, sex and calendar year, will be calculated using the Actuarial Society of South Africa's 2008 full model (ASSA2008).[95] The SMR calculation allows for a comparative analysis of mortality ratios between former asbestos miners and the general population, enabling the evaluation of the excess mortality hypothesised within the asbestos miner cohort. The SMRs will be presented in a separate results table (Table 3).

6.3 Cox Regression Analysis

Survival analysis will be employed to investigate the predictors of time-to-mortality risk in the asbestos miner cohort. Survival time will be computed as the total number of days from the date of the initial Trust examination and either the date of death or the censoring date (21 March 2023) for surviving participants. For participants with missing follow-up data, the last date on which they were known to be alive will be recorded as the censoring date in survival analysis.

A Cox proportional regression model will be utilised to identify sociodemographic, occupational, and clinical predictors associated with time-to-mortality while adjusting for relevant covariates. The Cox Hazard Regression analysis will include the predictor variables for mortality that will be significant at the 1% level ($p<0.01$) in the univariate regression analysis. A forward and backward stepwise selection technique will be used to build models and select the most important variables based on clinical relevance, statistical significance, and model fit criteria. Potential confounding variables (e.g., age, smoking, co-morbidities and sex) will be considered at this stage. Model fit criteria (AIC) will be used to compare models and select the best-fitting one. Adjusted Hazard Ratios (aHRs) with 95% confidence intervals will be reported to quantify the instantaneous risk of mortality associated with each significant predictor. The validity of the model and the proportionality assumption will be assessed statistically and graphically using Schoenfeld residuals.

6.4 Mortality Trends

This study will investigate mortality patterns among the cohort of former asbestos miners by computing the crude mortality rate for each year of the study period and for the duration of exit from asbestos employment. These crude mortality rates will be presented graphically in Figure 2 and 3 and will be used to elucidate epidemiologically significant temporal variations in mortality risk.

6.5 Management of Missing Data

The management of missing data will be guided by a comprehensive evaluation of missingness patterns. Following this analysis, a data cleaning strategy that incorporates error correction, a data imputation technique or deletion will be employed, based on the nature and extent of missingness.

6.6 Dummy Tables

See Tables 5-13 in appendices for dummy tables.

7. ETHICS

The research will be conducted in accordance with the guidelines outlined by the Belmont Report and Declaration of Helsinki. The study is categorised as low risk to the participants

7.1 Autonomy

As this will be an analysis of anonymised secondary data retrospectively spanning 20 years, the requirement for individual informed consent is non-applicable. Permission for the use of these data has been given by the Trust. Written informed consent was obtained from participants upon entry to the database which included consent for their data to be used in future research.

7.2 Confidentiality

To ensure participant anonymity, a process of de-identification will be implemented, employing a unique identifier system to distinguish data points. Trained researchers will then encode the data for secure storage on a password-protected electronic database. Access to this database will be restricted to authorised researchers only. In accordance with the established data governance protocols delineated by the School of Public Health and Family Medicine at the University of Cape Town, all electronic data will be maintained with the utmost confidentiality. To safeguard participant privacy during public or academic presentations, solely summarised data devoid of any personally identifiable information will be disseminated.

7.3 Beneficence

While this study design does not offer direct benefits to individual participants, a significant group benefit will be realised through the accrual of enhanced knowledge regarding asbestos-related mortality rates and associated risk factors. This knowledge will be instrumental in informing the optimisation of medical surveillance programs for former asbestos miners. Specifically, the findings will guide the development of targeted protocols encompassing the frequency of medical assessments and the most effective investigative procedures. By enabling the identification of high-risk individuals, this optimised surveillance approach will facilitate the early detection of asbestos-related diseases. Early detection will, in turn, pave the way for prompt referral to appropriate medical, psychological, and socioeconomic support services. This comprehensive approach has the potential to significantly improve the quality of life for former asbestos miners. Furthermore, the data generated by this study can serve as a powerful advocacy tool aimed at securing increased compensation for this vulnerable subgroup within the mining population.

7.4. Non-maleficence

The study poses no risk of any harm to participants.

7.5 Justice

The study intends to understand the mortality experience of this group which may inform measures to manage the surveillance, disease burden and compensation. Therefore, asbestos-exposed miners will ultimately benefit from this study**.**

8. LIMITATIONS

This research study is subject to potential limitations that could influence the validity and generalisability of its findings.

Information Bias

<u>Language limitation of literature search</u>

The literature search was limited to English articles; therefore, the possibility exists that relevant literature in other languages were missed. However, this does not impact on the validity of the study.

<u>Retrospective nature of the study</u>

Over the course of this retrospective study spanning 20 years, the Trusts' medical evaluation form was changed to incorporate an updated dypnoea grading system. The questions introduced were linked to the validated MMRC grading system and were very similar to the previous forms. Minor inconsistencies could have resulted, but the overall reliability of the tool was maintained.

In general, retrospective studies are prone to recall bias and therefore the possibility exists that information was missing or inaccurate. A data management plan was formulated by the researchers which included error correction, data imputation or deletion. Handling of missing data will be informed by an analysis of the nature and extent of missingness.

<u>The use of secondary data</u>

While the use of secondary data has the advantage of convenience and cost-efficiency, its use resulted in limited control over the nature and quality of the predictor variables. Hence the study was based on and limited to data collected and recorded on the database. Data on most predictors of interest were captured.

However, racial ascription which is essential for the computation of the SMR was not captured. If the SMR is calculated without the consideration of race its accuracy could be affected.

Self-reported data

The inherent reliance on self-reported medical and occupational histories introduces the possibility of recall bias. Despite the quality control measures employed to verify the data collected e.g., occupational records, medical records where available (see Table 1), participants may unintentionally misreport past events, leading to under- or overestimation of the exposure and mortality outcomes.

Data capture

While standardised forms and trained data capturers were employed, transcription errors remain a possibility. Furthermore, data capturing was not checked by the Trusts' medical co-ordinator.

Measurement bias

Although quality control measures were implemented to ensure the quality of spirograms and CXRs e.g., quality checks of the spirogram and CXR, two independent readers trained in the ILO classification, review by a second panel (see Table 1), the potential for information bias due to measurement error still exists. The SOMP evaluators interpreted the CXRs with full knowledge of the participant's medical, occupational, and smoking history. Reporting bias and misclassification could potentially have been introduced.

Lack of exposure intensity data

No accurate quantitative data on the intensity and hence cumulative dose of exposure were available. While duration of exposure is often considered a key predictor of adverse asbestos-related health outcomes, the absence of precise data on intensity introduces a potential confounding variable. If participants with shorter durations were exposed to higher intensities, the relationship between duration and asbestos-related health outcomes could be confounded. This study utilises calendar year of entry into asbestos employment and type of mine work as proxies for exposure intensity. However, these proxies may not perfectly capture the true intensity.

Selection Bias

The Healthy Worker Effect

The study design is susceptible to selection bias arising from the Healthy Worker Effect. Chronically or severely ill asbestos miners would have exited mine employment prematurely or died prior to the establishment of the Trust, resulting in a healthier remaining workforce. This differential selection based on health status would lead to an underestimation of mortality rates and influence of predictor variables.

Limitations of Mortality Data

Incompleteness of death reporting

The historical fragmentation, inconsistency, and inaccuracy of the South African death registration system prior to 2001,[87] raises concerns about the completeness of death reporting. While significant improvements have been made, the possibility of missed deaths and consequent underestimation of mortality rates cannot be disregarded.

Inaccurate cause-of-death data

The unreliability of cause-of-death information on the Home Affairs database restricted the analysis to all-cause mortality rates, preventing the investigation of cause-specific mortality associated with asbestos exposure. Cause-specific mortality rates would have provided more informative data in evaluating the relationships between predictor variables and mortality. The mortality data do not therefore necessarily reflect the incidence of an asbestos-related disease or other disease of relevance.

Generalisability

Representativeness of the ART/Kgalagadi cohort

The Trust's Inyosi database excludes mines that did not contribute financially to the ART and Kgalagadi Trust. However, the Trusts a sizeable proportion of former asbestos-exposed South African miners and therefore can be considered representative of the greater South African asbestos miner population. The generalisation of findings to the broader population of former South African asbestos miners can therefore be done with reasonable confidence. Furthermore, the representativeness of the ART and Kgalagadi cohort is likely skewed towards low-employment-grade miners relative to high-employment-grade miners. Generalisation of findings to low-employment grade miners employed during the study period can therefore be made with more confidence, while inferences to high-employment grade workers should be interpreted with circumspection.

Nationality restriction

The study's focus on South African miners necessitates caution when extrapolating findings to neighbouring countries where asbestos was mined, notably Eswatini and Zimbabwe, due to differences in the populations and occupational risk in their working environments, including asbestos fibre type.

These limitations highlight the need for careful interpretation of the mortality data and underscore the importance of considering these factors critically when drawing conclusions about the mortality experience of former South African asbestos miners.

9. DISSEMINATION OF RESEARCH RESULTS

The results of the study will be disseminated in the form of:

- A MMed dissertation which will be submitted to the University of Cape Town.
- Research forums, research days and local/international conferences
- Publications in scientific journals (local and peer-reviewed).

10. FUNDING

No funding is required for this study. The study was approved by the Asbestos and Kgalagadi Relief Trust Board, after the submission of a research synopsis by the principal investigator

11. TIMELINES

A Gantt Chart below estimates timelines for specific activities of the research study.

TABLE 7: Gantt Chart

Activity	Year 2024											
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Literature search	■											
Literature review/write-up		■	■									
Protocol write-up			■	■	■	■	■					
Ethics approval submission							■	■				
Data analysis								■	■	■		
Compilation of tables									■	■		
Dissertation write-up										■	■	
Dissertation submission											■	■

DUMMY TABLES

TABLE 2: Sociodemographic and health characteristics of Asbestos and Kgalagadi Relief Trust claimants with crude mortality rates for period 2004 to 2023

Characteristic	Alive (n/N) %	Deceased (n/N) %	Crude Mortality Rate (per 1000 person-years)	p-value	95% CI
Total (N)					
Age at initial examination (years)					
* 15 - 24.9					
25 - 34.9					
35 - 44.9					
45 - 54.9					
55 - 64.9					
≥ 65					
Biological Sex					
* Female					
Male					
Previous TB/Current TB					
* No					
Yes					
Smoking status#					
* Never					
Previous					
Current					
Comorbidities					
HIV positive					
* No					
Yes					
Asthma/COPD					
* No					
Yes					
Diabetes					
* No					
Yes					
Cardiovascular disease					
* No					
Yes					
Hypertension					
* No					
Yes					
Previous chest trauma					
* No					
Yes					
Other comorbidities					
* No					
Yes					

*Reference category
#Smoking categories: Never: Never smoked/smoked<6 months
Previous: Smoked > 6 months but stopped
Current: Still smoking at present

TABLE 3: Occupational characteristics of Asbestos and Kgalagadi Relief Trust claimants with crude mortality rates for period 2004 to 2023

Characteristic	Alive (n/N) %	Deceased (n/N) %	Crude Mortality Rate (per 1000 person-years)	p-value	95% CI
Total (N)					
Type of asbestos exposure					
* Chrysotile only					
Amosite only					
Crocidolite only					
Mixed					
Occupational category					
* Surface only					
Underground only					
Underground and surface					
Unspecified					
Mixed Mining exposures					
*Absent					
Present					
Mine Location					
*Kuruman area mines					
Penge mine					
Msauli mine					
Other					
Age on entry to asbestos employment (years)					
*15 - 24.9					
25 - 34.9					
35 - 44.9					
45 - 54.9					
55 - 64.9					
≥ 65					
Age at exit from asbestos employment (years)					
*15 - 24.9					
25 - 34.9					
35 - 44.9					
45 - 54.9					
55 - 64.9					
≥ 65					
Time in asbestos employment (years)					
*0 - 4.9					
5 - 9.9					
10 -14.9					
15 -19.9					
20 - 24.9					
≥25					
Calendar year of entry into employment (years)					
* After 2000					

1990 – 1999	
1980 - 1989	
1970 - 1979	
before 1970	
Calendar year of exit from employment (years)	
*After 2000	
1990 - 1999	
1980 - 1989	
1970 - 1979	
before 1970	
Time since exit from employment (years)	
*0 - 4.9	
5 - 9.9	
10 -14.9	
15 -19.9	
20 - 24.9	
≥25	
*Reference category	

TABLE 4: Clinical characteristics of Asbestos and Kgalagadi Relief Trust claimants at initial examination with crude mortality rates for period 2004 to 2023

Characteristic	Alive (n/N) %	Deceased (n/N) %	Crude Mortality Rate (per 1000 person-years)	p-value	95% CI
Total (N=)					
Clinical Symptoms					
Dyspnoea					
*Absent					
Present					
Dyspnoea Grade#					
*MMRC 0					
MMRC I					
MMRC II					
MMRC III					
MMRC IV					
Clinical Examination					
BMI at baseline (kg/m^2)^					
*Normal					
Underweight					
Overweight					
Obese					
Physical examination!					
*Normal					
Abnormal					
Signs of cardiac failure£					
*Absent					
Present					

*Reference category

MMRC Classification: MMRC 0: Breathless on strenuous exercise
MMRC I: Breathless on hurrying/walking uphill
MMRC II: Slower than peers/need to stop
MMRC III: Breathless after few minutes/ walking 100m
MMRC IV: Breathless on dressing/undressing
MMRC II-IV considered significant dyspnoea

$ Significant weight loss defined as a 5% reduction in weight from baseline within a 6–12-month period

^ BMI categories: Underweight < 18.5 kg/m2
Normal = 18.5 to 24.9 kg/m2
Overweight = 25 to 29.9 kg/m2
Obese ≥ 30 kg/m2

! Abnormal respiratory examination defined as the presence of any of the following features: clubbing, cyanosis, crackles n auscultation, an
increased respiratory rate or decreased SaO2% (Table 1 details operationalisation of variables)

£ Signs of cardiac failure included a raised pitting peripheral oedema, displaced apex, a raised JVP, and S3 gallop. The presence of any or all the signs was regarded as positive

TABLE 5: Radiological data of Asbestos and Kgalagadi Relief Trust claimants at initial examination with crude mortality rates for period 2004 to 2023 (as per ILO Classification)

Characteristic	Alive (n/N) %	Deceased (n/N) %	Crude Mortality Rate (per 1000 person-years)	p-value	95% CI
Total (N=)					
ILO Profusion Categories#					
* Category 0					
Category 1					
Category 2					
Category 3					
Pleural abnormalities$					
*Absent					
Present					
Pleural plaques					
*Absent					
Present					
Costophrenic angle obliteration					
*Absent					
Present					
Diffuse pleural thickening					
*Absent					
Present					
Lung Cancer					
*Absent					
Radiological suspicion					
Histological evidence					
Mesothelioma					
*Absent					
Radiological suspicion					
Histological evidence					
Other radiological findings					
*Absent					
Present					

*Reference category

ILO profusion categories: Category 0: 0/-; 0/0/; 0/1
Category 1: 1/0; 1/1; 1/2
Category 2: 2/1; 2/2; 2/3
Category 3: 3/2; 3/3; 3/+
Categories 2-3 were considered abnormal

$ Pleural abnormalities reported included pleural plaques, costophrenic angle obliteration, diffuse pleural thickening. Pleural abnormalities were categorised as binary i.e., absent or present.

Other radiological abnormalities include

TABLE 6: Spirometry data of Asbestos and Kgalagadi Relief Trust claimants at initial examination with crude mortality rates for period 2004 to 2023

Characteristic	Alive (n/N)%	Deceased (n/N)%	Crude Mortality Rate (per 1000 person-years)	p-value	95% CI
Total (N=)					
Spirometry Parameters#					
FEV_1/FVC ratio (%)					
FVC (litres)					
FEV_1 (litres)					
FEV_1/FVC ratio					
*Normal					
Low					
FVC					
*Normal					
Low					
FEV_1					
*Normal					
Low					
Lung function categories#					
*Normal					
Abnormal					
Obstructive lung defect					
*Absent					
Present					
Obstructive lung defect					
Mild					
Moderate					
Moderately severe					
Severe					
Very Severe					
Restrictive lung defect					
*Absent					
Present					
Restrictive lung defect					
Mild					
Moderate					
Moderately severe					
Severe					
Very Severe					
Mixed lung defect					
*Absent					
Predominantly obstructive					
Predominantly restrictive					

*Reference category
Spirometry parameters and lung function were categorised using the GLI reference equations (see Table 1)

TABLE 7: **Standardised mortality ratios (SMR) of asbestos relief claimants relative to the general South African population matched for sex, age and calendar year**

Characteristic	Observed deaths	*Expected deaths	SMR	95% CI
Biological Sex				
Male				
Female				
Age (years)				
20-24.9				
25-29.9				
30-34.9				
35-39.9				
40-44.9				
45-49.9				
50-54.9				
55-59.9				
60-64.9				
65-69.9				
>70				
Calendar year				
2004				
2005				
2006				
2007				
2008				
2009				
2010				
2011				
2012				
2013				
2014				
2015				
2016				
2017				
2018				
2019				
2020				
2021				
2022				

*****ASSA2008 used for population references

TABLE 8: Sociodemographic predictors of mortality in Asbestos and Kgalagadi Relief Trust claimants for period 2004 to 2023

Predictor	Estimate of β	Standard error of β	Adjusted Hazard Ratio	95% CI	p-value
Age at initial examination (years)					
* 15 - 24.9					
25 - 34.9					
35 - 44.9					
45 - 54.9					
55 - 64.9					
≥ 65					
Biological Sex					
* Female					
Male					
Previous TB/Current TB					
* No					
Yes					
Smoking status*					
* Never					
Previous					
Current					
Comorbidities					
HIV positive					
* No					
Yes					
Asthma/COPD					
* No					
Yes					
Diabetes					
* No					
Yes					
Cardiovascular Disease					
* No					
Yes					
Previous chest trauma					
* No					
Yes					
Other comorbidities					
* No					
Yes					

<u>TABLE 9:</u> Occupational predictors of mortality in Asbestos and Kgalagadi Relief Trust 's claimants for period 2004 to 2023

Predictor	Estimate of β	Standard error of β	Adjusted Hazard Ratio	95% CI	p-value
Type of asbestos exposure					
* Chrysotile only					
Amosite only					
Crocidolite only					
Mixed					
Occupational category					
* Surface only					
Underground only					
Underground and surface					
Unspecified					
Mixed mining exposures					
*Absent					
Present					
Mine Location					
Kuruman area mines					
Penge mine					
Msauli mine					
Other mines					
Age on entry into asbestos employment (years)					
*15 - 24.9					
25 - 34.9					
35 - 44.9					
45 - 54.9					
55 - 64.9					
≥ 65					
Age at exit from asbestos employment (years)					
*15 - 24.9					
25 - 34.9					
35 - 44.9					
45 - 54.9					
55 - 64.9					
≥ 65					
Time in asbestos employment (years)					
* 0 - 4.9					
5 - 9.9					
10 -14.9					
15 -19.9					
20 - 24.9					
≥25					
Calendar year of exit from employment (years)					

*1998 – 2002
1993 - 1997
1988 - 1992
1983 - 1987
1978 –1982
Time since exit from employment (years)
*0 - 4.9
5 - 9.9
10 -14.9
15 -19.9
20 - 24.9
≥25
*Reference category

TABLE 10: Clinical predictors of mortality in Asbestos and Kgalagadi Relief Trust claimants for period 2004-2023					
Predictor	**Estimate of β**	**Standard error of β**	**Adjusted Hazard Ratio**	**95% CI**	**p-value**
Symptoms					
Dyspnea (MMRC grade)[@]					
* MMRC 0					
MMRC I					
MMRC II					
MMRC III					
MMRC IV					
Physical examination					
BMI (kg/m^2)[β]					
* Normal					
Underweight					
Overweight					
Obese					
Respiratory examination[!]					
* Normal					
Abnormal					
Signs of cardiac failure[£]					
*Absent					
Present					
Radiological data					
ILO profusion category[#]					
*Category 0					
Category 1					
Category 2					
Category 3					
Pleural abnormalities[$]					
*Absent					
Present					
Pleural plaques					
*Absent					
Present					
Costophrenic angle obliteration					
*Absent					
Present					
Diffuse pleural thickening					
*Absent					
Present					
Lung cancer					
*Absent					
Radiological suspicion					
Histological evidence					
Mesothelioma					
*Absent					
Radiological suspicion					

Histological evidence

Spirometry Data[ε]
Spirometry parameters
FEV_1/FVC ratio (%)
FVC (litres)
FEV_1 (litres)

FEV_1/FVC ratio
*Normal
Low
FEV_1
*Normal
Low
FVC
*Normal
Low
Spirometry categorisation[ε]
*** Normal lung function**
*Absent
Present
Obstructive lung defect
*Absent
Present
Obstructive lung defect
*Mild
Moderate
Moderately severe
Severe
Very severe
Restrictive lung defect
*Absent
Present
Restrictive lung defect
*Mild
Moderate
Moderately severe
Severe
Very severe
Mixed ventilatory defect
* Absent
Predominantly obstructive
Predominantly restrictive

Clinical parameters recorded at baseline examination
* Reference category
[@] MMRC Classification: MMRC 0: Breathless on strenuous exercise
MMRC I: Breathless on hurrying/walking uphill
MMRC II: Slower than peers/need to stop
MMRC III: Breathless after few minutes/ walking 100m
MMRC IV: Breathless on dressing/undressing

MMRC II-IV considered significant dyspnoea

^ Significant weight loss defined as a 5% reduction in weight from baseline within a 6–12-month period

β BMI categories: Underweight < 18.5 kg/m2
Normal = 18.5 to 24.9 kg/m2
Overweight = 25 to 29.9 kg/m2
Obese ≥ 30 kg/m2

! Abnormal respiratory examination defined as the presence of any of the following features: clubbing, cyanosis, crackles n auscultation, an increased respiratory rate or decreased SaO2% (Table 1 details operationalisation of variables)

£ Signs of cardiac failure included a raised pitting peripheral oedema, displaced apex, a raised JVP, and S3 gallop. The presence of any or all the signs was regarded as positive

ILO profusion categories: Category 0: 0/-; 0/0/; 0/1
Category 1: 1/0; 1/1; 1/2
Category 2: 2/1; 2/2; 2/3
Category 3: 3/2; 3/3; 3/+
Categories 2-4 were considered abnormal

$ Pleural abnormalities reported included pleural plaques, costophrenic angle obliteration, diffuse pleural thickening. Pleural abnormalities were categorised as binary i.e., absent or present.

ε Spirometry data and lung function categorisation based on GLI reference values (see Table 1)

TABLE 11: Number of deaths, person years, and crude mortality rates of former South Africa miners for each year of the study period

Calendar year	No. of deaths	Person-years (1 000s)	Mortality rate/ 1 000 person-years	95% CI
2004				
2005				
2006				
2007				
2008				
2009				
2010				
2011				
2012				
2013				
2014				
2015				
2016				
2017				
2018				
2019				
2020				
2021				
2022				
Total				

* Table 12 represented graphically as Figure 2

<u>TABLE 12</u>: Number of deaths, person years, and mortality rates of former South Africa miners by time since exit from asbestos employment

Time since exit (years)	No. of deaths	Person-years (1 000s)	Mortality rate/ 1 000 person-years	95% CI
0-0.9				
1-1.9				
2-2.9				
3-3.9				
4-4.9				
5-5.9				
6-6.9				
7-7.9				
8-8.9				
9-9.9				
10-10.9				
11-11.9				
12-12.9				
13-13.9				
14-14.9				
15-15.9				
16-16.9				
17-17.9				
18-18.9				
19-19.9				
>20				
Total				

* Table 13 represented graphically as Figure 3

FIGURE 1: Schoenfield residuals

FIGURE 2: Crude mortality rate for former asbestos miners by calendar year for each year of the study

FIGURE 3: Crude mortality rate for former asbestos miners by year of exit from the industry

Appendix 2: Medical Evaluation Form

ART & KRT Medical Evaluation Form 2023

Diagnostic Medicine Page 1

Surname		First Name/s	
ID # or Passport #	Fill in birthdate only if no ID #	Birthdate: ccyy-mm-dd	
Contact Address			
Contact #'s			

Preferred Language/s	1	2	3	4	Other:

Afrikaans A, Setswana B, English E, Sesotho L, Ndebele N, Sepedi P, Swati S, Tsonga T, Venda V, Xhosa X, Zulu Z.

OCCUPATIONAL HISTORY *list all jobs including times of limited employment and self-employment*

#	Employer / Company Name	Job Name	Year Began	Year Ended	Total Time
1					
2					
3					
4					
5					
6					

ENVIRONMENTAL – Indicate the 2 main types of fuel by writing "1" as main and "2" as second

What type of fuel do you use:	Electricity	Paraffin	Gas	Wood	Coal stove	Imbawula	Other - specify	
for cooking?								
for indoor heating?								or None

SMOKING HISTORY (Circle as apt, or write)

Cigarettes:	NEVER SMOKED < 20 packs of cigarettes ever	Age Started	Age Ended	No. of Years Smoking	Ave #/day
Pipe or Other	EX-Smoker				
	CURRENT Smoker		*Currently smoking*		

ADL ☑ *Least able*	Walking	Bathing, mouth care	Toilet use	Dressing & Grooming	Getting in & out: bed/chair/taxi	Feeding	Going up stairs
Can do							
Needs help							
Dependent							
Cannot do							
	A	B	C	D	E	F	G

CURRENT & PAST ILLNESSES	Year/s Diagnosed	List all treatment
Tuberculosis (TB)		
HIV		
Asthma / COPD		
Cardiac		
Diabetes		
Hypertension		
Chest scar (Surgery/Stab/Fracture/Injury)		
Other chest condition/s:		

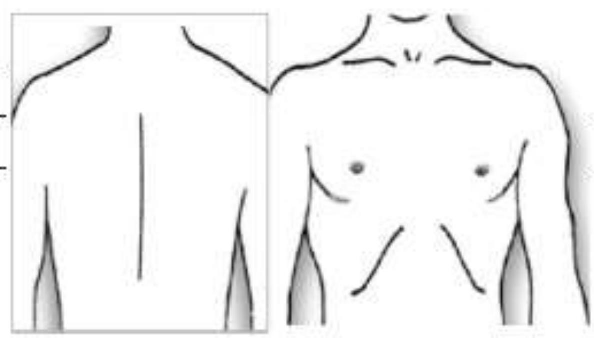
Diagnostic Medicine

SYMPTOMS	Duration plus Detail				
Cough – when, dry/wet, blood?					
Loss of Weight					
Dyspnoea scale	Only on strenuous exercise	When hurrying on the flat or walking slight uphill	Walks slower than most on the level, stops after ~1.5 km, or after 15 minutes at own pace	Stops for breath after ~100 m or after a few minutes' walk on level ground	Too breathless to leave the house or breathless when undressing
If walking, what makes you slow or stop?		Chest Pain	Breathlessness	Leg Pain	Other ↓
Other symptoms including chest pain and type					

MEDICAL EXAMINATION *Examine with shoes and shirt off*

BP		WGT kg	HGT cm shoes off	
Appearance	Well Unwell Very Sick		Cyanosis Adenopathy Clubbing Ankle oedema	

	Look, Touch, Tap, Listen (with shirt off)	
Cardiac **Pulse Rate** (+ Rhythm if Abnormal)		**Chest** **Breath Rate** (N 12-16)
SaO₂%		**Breathless?** yes no
Signs of RV or LV failure?		**Hyperinflated?** yes no



NB - Note or sketch:
Any Shape Abnormality; Site of Scars; Dullness/Stony Dullness; Inspiratory or Expiratory: Crackles/Rubs/Wheezes; Liver palpable

Specify any other notable findings

Examining Clinician's summary assessment
(e.g. Unwell, thin man with poorly controlled HT)

Date

Sign

Any other notes

Appendix 3: Specialised Occupational Medicine Panel (SOMP) Data Collection Form

Inyosi # and File #

SOMP Reading for ART / KRT

Counter #

ID #		Age ~ yrs 70 · Hgt cm 170 · BMI
Name	SOMP FORM	m · Wgt kg 70 · 24.2

From	Dr		
Repeat	Unbid	Digital	

Medical Exam Quality	1	2	3	4
(Default is Quality 1) Legible, all areas filled, no contradictions	All criteria met	Few departures	Hard to interpret, missing items, but usable	Not usable /blank

↓ Date: 01 Jan 2024

Overexposed Too dark	Underexposed Too light
Underinspired	Improper Position
Poor contrast	Artefacts
Poor processing	Mottle
Scapula overlay	Excessive edge enhancement
Other (specify):	

CXR	Quality	LFT		
1	Good, all criteria met	1	Non crisp start	<3 acceptable blows
2	Few technical defects	2	Poor PEF peaking	FVC parity >150ml
3	Defects; but can classify	3	Downslope bumpy	FEV_1 parity >150ml
4	Unreadable	4	Non-level End	FVC / FVC non-parity
	(Mark all unmet criteria) (Default is quality 1)		Other (specify):	BEV > 5% FVC

5% FVC 200 ml

ECCS	FVC	FEV_1
Predicted	3.69	2.79
Measured	4.00	3.00
% predicted	108	107
Ratio %		75

Date ↓ 01 Jan 2024

Occupational

Asbestos Mining ccyy-ccyy

Time in Asbestos Mining

Main mine/s

Main Job/s

Prior certification & Year

Death date (if)

2 Any *classifiable* parenchymal abnormalities?

Profusion must be shown

If > 0/0, show Zones & Shape/Size

SMALL ▼ ... ▼ LARGE

Zones		Shape/ Size							Profusion				
									0/-	0/0	0/1		
RU	LU	1°	p	q	r	s	t	u	1/0	1/1	1/2	A	>1cm <5cm
RM	LM	2°	p	q	r	s	t	u	2/1	2/2	2/3	B	All Ø Σ >5cm <RUZ area
RL	LL		Rounded			Irregular			3/2	3/3	3/+	C	Summed area is >RUZ area

p/s ≤1.5mm; q/t ≤3mm; r/u ≤10mm

Show in diagram below

N	
Normal Mild Moderate Severe	Obstructive Mixed Restrictive

Assessment & Comments:

3 Any *classifiable* pleural abnormalities? YES Mark as apt NO

a	b	c			Pleural Plaques			c	b	a
3			u	C	In-profile	C	u			3
2	R		u	C	Face-on	C	u	L		2
1			u	C	Diaphragm*	C	u			1
			u	C	Other*	C	u			

Use width/abc for in-profile only:

a ~3-5, b ~5-10, c ~10+ mm wide

For extent/height/123, sum in-profile & face-on

1 ≤ ¼; 2 >¼ ≤ ½; 3 > ½ of lateral chest wall

u/C = un-/Calcified; *No extent/width needed

Yes — Costophrenic angle obliteration? — Yes

R — Diffuse pleural thickening (DPT) — L

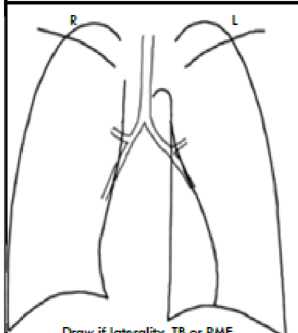
DPT occurs in costophrenic angle obliteration, CPAO

The lower limit of CPAO is defined by the Pleural, CPAO image

4 Any other abnormalities?

Other diseases, abnormalities, or comments. Symbols must be marked

YES Mark as apt NO



Draw if laterality, TB or PMF

Symbols			
aa	at	ax	be
br	bu	CA	cg
cn	co	cp	cv
di	EF	em	es
fr	hi	ho	id
ih	kl	ME	pa
pb	pi	px	ra
rp	sc		TB

be bronchiectasis

br bronchial wall thick

sc spinal curvature

Should worker see personal physician because of findings in this section? YES NO

Relevant History & Examination

Smoking		Past PTB	
Rx			
Sx			
Ex			
Summary			

Plan	re-SOMP	to EMP	Referral letter	Referral email	More tests	for MBOD	Medical Letter	Social/ 14.2 Help
	1	2	3	4	5	6	7	8
Specify further actions - What and When	2024	2025	2026	Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec				

REPEAT	for account of		
CXR	Doctor	TRUST	Client
LFT	Doctor	TRUST	Client
EXAM	Doctor	TRUST	Client

2024	Read date	No ARD (N)	Not Trust payable (N)	⌛	ARD 1	ARD 2	ARD 3 Lung Cancer	ARD 4 Mesothelioma

Medical specialist signatures > Radiologists *

Mark if done solo

Appendix 4: Consent Form on Admission to Trust Database

ASBESTOS RELIEF TRUST

KGALAGADI RELIEF TRUST

AUTHORIZATION

I hereby authorise the Trustees to obtain copies of my medical records at the MBOD and or the CCOD.

I also authorise my ex and or current employer to make available to the Trustees copies of any documentation from my personal file which they may require in considering this application.

I agree, in the event that an award is made to me, to sign the appropriate Release and Discharge form, in order to receive any compensation due to me.

By participating in this process, I understand that my records MAY be used along with the records of other claimants for reporting, statistical and research purposes. The Asbestos Relief Trust/Kgalagadi Relief Trust undertakes to maintain the confidentiality and anonymity of my records at all times when used for such purposes.

I confirm that to the best of my knowledge and belief, the information contained in this application is true and correct.

Signed at Johannesburg on the 21 day of August 2006

Claimant Authorised Representative

....

Witnesses:

....

.......SNkoyi.......................

Date: 21 AUG 2006

Appendix 5: Data Transfer Agreement

DATA TRANSFER AGREEMENT BETWEEN THE ASBESTOS AND KGALAGADI RELIEF TRUSTS AND RESEARCHERS AT THE UNIVERSITY OF CAPE TOWN

Data Transfer Agreement

This Agreement is made and entered into as of 01 February 2024 by and between:

1. The Asbestos and Kgalagadi Relief Trusts
(Hereinafter referred to as the "Data Provider")
Address: Sherborne Square – Building One, 5 Sherborne Road, Parktown, 2193

Represented by The Chairs: Mr Connie Molusi and Mr Brian Gibson
Contact Information: connie@molusi.com and gibson@icon.co.za

2. The University of Cape Town
(Hereinafter referred to as the "Data Recipient")
Address: School of Public Health, Level 4, Falmouth Building, University of Cape Town
Represented by: Associate Professor S Adams, Prof R Ehrlich and Dr. Y Williams
Department: Division of Occupational Medicine
Contact Information: shahieda.adams@uct.ac.za
rodney.ehrlich@uct.ac.za
yumna.williams-mohamed@westerncape.gov.za

1. Purpose of the Agreement

The Data Provider agrees to transfer specific data to the Data Recipient for the purpose of conducting research on "An evaluation of mortality rates and their determinants in a cohort of former asbestos-exposed miners". The data provided will be used solely for this research and in accordance with the terms outlined in this Agreement.

2. Description of the Data

The data to be transferred under this Agreement includes anonymised vital status, sociodemographic, occupational and clinical data which includes participants' background medical history, occupational and asbestos exposure history, clinical examination findings and radiological and lung function data. The data may include personal, sensitive, or confidential information.

3. Obligations of the Data Provider

The Data Provider shall supply the Data Recipient with the data in electronic format (a password-protected Excel spreadsheet) by 15 September 2024.

The Data Provider warrants that it has the right to transfer the data and that the data is accurate and complete to the best of its knowledge.

4. Obligations of the Data Recipient

The Data Recipient agrees to use the data only for the purpose of the research specified in this Agreement.

The Data Recipient shall ensure that the data is stored securely and that access to the data is limited to authorised personnel involved in the research.

The Data Recipient shall not disclose the data to any third party without the prior written consent of the Data Provider.

The Data Recipient agrees to comply with all applicable laws and regulations regarding data protection and privacy.

5. Confidentiality
Both parties agree to maintain the confidentiality of the data. The Data Recipient shall not use the data for any purpose other than the research outlined in this Agreement and shall not disclose the data to any unauthorised person.

6. Intellectual Property
The Data Provider retains ownership of the data. Any intellectual property arising from the research conducted using the data shall be owned by the Data Recipient, subject to any terms agreed upon by both parties.

7. Publication
The Data Recipient may independently publish the results of the research, provided that the Data Provider is acknowledged in any publications. The Data Recipient shall provide the Data Provider with a copy of any publication arising from the use of the data before submission for publication.

8. Termination
This Agreement shall remain in effect until the 30 July 2025 or until the research is completed, whichever comes first. Upon termination, the Data Recipient shall return or destroy all copies of the data, as requested by the Data Provider.

9. Governing Law
This Agreement shall be governed by and construed in accordance with the laws of South Africa.

10. Signatures
For the Data Provider:

1. ____________________ 20/09/2024
   Mr C Molusi — Date
2. ____________________ 20/09/2024.
   Mr B Gibson — Date

For the Data Recipient:

1. sadams — 30/09/2024
   Associate Professor Shahieda Adams — Date
2. ____________________ 01.10.2024
   Professor Rodney Ehrlich — Date
3. ____________________ 03/09/2024
   Dr. Yumna Williams-Mohamed — Date

NC

Nadia Ebrahim Digitally signed by Nadia Ebrahim Date: 2024.10.31 11:32:54 +02'00'

Appendix 6: HREC Ethics Approval Letter by UCT Faculty of Health Science

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/home/human-research-ethics

14 November 2024

HREC REF: 625/2024

A/Prof S Adams
Public Health & Family Medicine
FHS
Email: shahieda.adams@uct.ac.za
Student: WLLYUM001@myuct.ac.za

Dear A/Prof Adams

PROJECT TITLE: AN EVALUATION OF MORTALITY RATES AND THEIR DETERMINANTS IN A COHORT OF FORMER ASBESTOS-EXPOSED MINERS-
(MMED IN OCCUPATIONAL MEDICINE-DR YUMNA WILLIAMS-MOHAMED)

Thank you for your response email dated 05 November 2024, addressing the issues by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 November 2025.

Please submit a progress form, using the standardised Annual Report Form (FHS016) or FHS017 if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Yumna Williams-Mohamed will also be involved in this study.

Please quote HREC REF 625/2024 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR MARC BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007

HREC/ref 625.2024

Appendix 7: Supplementary information not in the manuscript

Table SI: Operationalisation of variables and quality control measures employed

Predictor variable	Variable definition	Quality control measures
Age at Initial Examination(years) < 35 35-44.9 45-54.9 55-64.9 >65	Calculated from the birth date on identity (ID) document and date of the initial baseline examination by medical officers employed by the Asbestos Relief and Kgalagadi Relief Trusts. Transformed into a categorical variable as indicated.	Verified birth date with ID document
Biological Sex Male Female	Biological sex of miner recorded by the clinician.	
Cigarette Smoking History Never Previous Current	Self-disclosed to the clinician. **Never:** Never smoked/smoked < 1 pack year. **Previous**: Smoked > 1 pack year but stopped **Current:** Still smoking at present.	
Type of Asbestos Exposure Crocidolite Amosite Chrysotile Mixed	Self-disclosed to the clinician if known	Verified by examining the occupational record and geographic mapping of mines
Time in Employment (years) < 5 5-10 10-15 >15 Unknown	Estimated from first and last date of service in the asbestos industry, where known.	Verified by examining occupational record, where possible
Nature of Mine Work Underground Surface Both Unspecified	Self-disclosed to the clinician. All types and levels of asbestos exposure were regarded as significant i.e. no minimum period of exposure was required.	Verified by examining occupational record where possible
Body Mass Index (kg/m^2) Underweight Normal Overweight Obese	BMI was calculated from the measured weight and height using the formula weight/height^2 (kg/m^2). BMI was categorised by researchers as outlined below: **Underweight**: < 18.5 kg/m^2 **Normal:** = 18.5 to 24.9 kg/m^2 **Overweight:** = 25 to 29.9 kg/m^2 **Obese:** ≥ 30 kg/m^2	Weight and height measurements performed in standardised manner**.**

Predictor variable	Variable definition	Quality control measures
Quality of CXR Good Few technical defects Defects but can classify Unreadable	The quality of the chest X-ray (CXR) was assessed prior to reading.	The quality of the CXR was assessed prior to the reporting and recording of data. The CXR was repeated if the initial one was unreadable.
Radiological Classification **ILO Profusion categories** Category 0 Category 1 Category 2 Category 3	Radiological data were reported in a standardised manner by radiologist and medical practitioners with experience and expertise in occupational medicine in accordance with International Labour Organisation (ILO) Classification of Radiographic Pneumoconioses.[21] ILO Profusion Categories: **Category 0**: 0/-; 0/0/; 0/1 **Category 1:** 1/0; 1/1; 1/2 **Category 2:** 2/1; 2/2; 2/3 **Category 3:** 3/2; 3/3; 3/+ Category 1-3 considered abnormal	Trained radiologists and medical practitioners with experience and expertise in occupational medicine were members of a Specialist Occupational Medicine Panel (SOMP) who captured physical examination, radiological and spirometry data on a standardised form. The radiographs were read with full knowledge of the patient's medical, occupational, or cigarette-smoking history. The classification of radiological data was done by consensus between the radiologist and the medical practitioner with the radiologist's reading prevailing. Where classification was difficult or borderline or where there was disagreement between the radiologist and occupational medicine specialist, a different SOMP panel was enlisted to classify the CXR. In such cases, the report of the SOMP panel making the higher classification was used.
Pleural abnormalities Pleural plaques Costophrenic angle obliteration Diffuse pleural thickening Absent Present	Pleural abnormalities were reported in accordance with the ILO Classification system and included pleural plaques, costophrenic angle obliteration, diffuse pleural thickening. Pleural abnormalities were categorised as binary i.e., absent or present. The hyperlink below provides a detailed explanation of the ILO Classification of Radiographs of Pneumoconioses 1980. **ILO classification**: (click for reference)	
Quality of the Spirogram Good Few technical defects Defects but can classify Unreadable	Spirometry was conducted by an experienced technician/medical officer. Spirometry results were recorded and categorised by a medical officer experienced in interpreting the quality and parameters of spirograms.	Spirometry was assessed in accordance with the current European Thoracic Society/American Thoracic Society (ERS/ATS) guidelines.[22, 23] Spirometer models producing good quality spirograms were used (Model IQ Tech and Koko). The quality of the spirogram was assessed and if deemed uninterpretable, the spirogram was repeated.
Spirometry Classification FEV_1 Normal FEV_1 Low	**FEV_1 Normal:** FEV_1 z-score ≥ -1.64 **FEV_1 Low**: FEV_1 z-score < -1.64 **Mild**: FEV_1 z-score: < -1.64 but > -2.0 **Moderate**: FEV_1 z-score: < -2.0 but > -3.0 **Severe**: FEV_1 z-score: ≤ -3.0	Global Lung Function Initiative (GLI) reference equations were used to generate FEV_1, FVC and FEV_1/FVC z-scores for each participant using their age, sex, height and raw FEV_1 and FVC values. The GLI-other ethnic category was used. A z-score cut-off ≥ -1.64 was used to dichotomise the FEV_1 and FVC raw values into normal and low categories. The GLI z-scores were

Predictor variable	Variable definition	Quality control measures
FVC Normal FVC Low	**FVC Normal:** FVC z-score ≥ -1.64 **FVC Low**: FVC z-score < -1.64 **Mild:** FVC z-score: < -1.64 but > -2.0 **Moderate:** FVC z-score: < -2.0 but > -3.0 **Severe:** FVC z-score: ≤ -3.0	used to further subcategorise FEV_1 and FVC as outlined.
Asbestos-Related Disease (ARD) Category **No** ARD ARD **1** ARD **2** ARD **3** ARD **4** **ARD not determined yet**	The Trusts used a composite classification system to categorise asbestos-related disease (ARD) in claimants. Both the radiological findings as per ILO classification and the spirometry results using the European Community for Steel and Coal (ECSC) reference values were used to categorise the claimants as follows[25]: **No ARD**: Spirometry: FEV_1 and FVC ≥ 80% FEV_1/FVC ratio ≥ 75% Radiology: No evidence of asbestosis/asbestos-related changes **ARD 1**: Asbestos-related pleural thickening/asbestosis with mild to moderate lung function impairment Spirometry: FEV_1 and FVC ≥ 52 but < 80% FEV_1/FVC ratio ≥ 55 but < 75% Radiology: ILO reading consistent with asbestosis/ asbestos-related changes **ARD 2**: Asbestos-related pleural thickening/asbestosis with severe lung function impairment Spirometry: FEV_1 and FVC < 52% FEV_1/FVC ratio < 55% Radiology: ILO reading consistent with asbestosis/ asbestos-related changes **ARD 3**: Asbestos-related lung cancer Based on histological evidence **ARD 4**: Mesothelioma Based on histological evidence For ARD 3 and 4, where histological evidence was not available, radiological diagnosis was made by a radiologist. Where asbestosis or pleural disease coexisted with malignancy, the higher ARD grade was used.	

Table SII: Observed deaths, total person years and crude mortality rates for each year of the study period from 2004 to 2023				
Calendar year	**Observed deaths**	**Total person-years**	**Crude Mortality Rate (/1 000 persons)**	**95% CI**
2004	11	395.09	27.84	11.39 - 44.30
2005	54	1 967.32	27.45	20.12 – 34.76
2006	178	5 851.50	30.42	25.95 – 34.89
2007	239	7 544.37	31.68	27.66 – 35.70
2008	285	8 146.61	34.90	30.92 – 39.05
2009	297	8 779.64	33.94	29.98 – 37.68
2010	335	9 067.06	36.73	32.99 – 40.90
2011	293	8 948.49	32.74	28.99 – 30.46
2012	286	8 769.35	32.61	28.83 – 37.24
2013	273	8 547.37	31.94	28.15 – 35.73
2014	301	8 315.42	36.20	32.11 – 40.29
2015	306	8 084.54	37.85	33.61 – 42.09
2016	317	7 892.39	40.17	35.74 – 44.59
2017	296	7 638.92	38.75	34.33 – 43.16
2018	318	7 505.81	42.50	37.71 – 47.02
2019	241	7 380.10	32.66	28.53 – 36.78
2020	296	7 152.65	41.83	36.67 – 46.10
2021	467	6 759.35	69.09	62.82 – 75.36
2022	264	6 409.62	41.19	36.22 – 46.16
till 21/03/2023	49	1 393.73	35.15	25.31 – 45.00
Total	**5106**	**136 548.92**	**37.39**	**36.37 – 38.41**

[*] Table SIII represented graphically as Figure 2

Table SIII: Results of Extended Cox Regression modelling covariates violating the proportional hazards assumption as time-varying

Main Effects			
Predictor	**Adjusted Hazard Ratio**	**95% CI**	**p-value**
Age on Entry to Cohort (years)			
*< 35	-	-	-
35 – 44.9	1.25	0.74 – 2.13	0.409
45 - 54.9	1.61	0.95 – 2.72	0.077
55 - 64.9	2.28	1.35 – 3.87	0.002
≥ 65	3.58	2.11 – 6.08	0.000
#Biological Sex			
* Female	-		
Male	1.05	0.96 - 1.14	0.293
Cigarette Smoking Status			
* Never	-	-	-
Previous	1.36	1.28 – 1.45	0.000
Type of Asbestos Exposure			
* Chrysotile only	-	-	-
Crocidolite only	1.07	0.99 – 1.16	0.081
Amosite	0.85	0.67 – 1.09	0.202
Mixed	1.18	0.86 – 1.62	0.313
Unspecified	1.19	1.09 – 1.31	0.000
Nature of Mine Work			
*Underground only	-	-	-
Surface only	1.07	0.99 - 1.16	0.074
Unspecified	0.82	0.66 – 1.01	0.062
Time in Employment (years)			
* 0 - 5	-	-	-
5 - 10	0.88	0.78 – 1.00	0.042
10 -15	0.83	0.63 – 1.09	0.182
>15	1.33	0.96 – 1.85	0.086
Unknown	1.09	1.00 – 1.19	0.040
BMI Categories at Baseline(kg/m^2)			
*Normal	-	-	-
Underweight	1.53	1.41 – 1.65	0.000
#Overweight	19.97	16.97 – 25.52	0.000
#Obese	22.84	17.28 – 25.15	0.000
ILO Profusion Categories			
* Category 0	-	-	-
Category 1	1.19	1.09 – 1.29	0.000
Category 2	1.32	1.07 – 1.62	0.009
Category 3	1.54	1.00 – 2.36	0.048
Pleural Plaques			
*Absent	-	-	-
Present	0.87	0.81 - 0.94	0.000
Costophrenic Angle Obliteration			
*Absent	-	-	-
Present	1.25	1.12 – 1.39	0.000

Predictor	Adjusted Hazard Ratio	95% CI	p-value
[#]Diffuse Pleural Thickening			
[*]Absent	-	-	-
Present	1.04	0.85 – 1.27	0.665
FEV_1 (litres)			
[*]Normal	-	-	-
Low FEV_1 z-score: -1.64 to -2.0	1.03	0.93 – 1.14	0.602
FEV_1 z-score: -2.0 to -3.	1.12	1.02 – 1.23	0.017
FEV_1 z-score: ≤ -3.0	15.02	12.43 – 18.16	0.000
FVC (litres)			
[*]Normal	-	-	-
Low FVC z-score: -1.64 to -2.0	1.00	0.90 – 1.12	0.947
FVC z-score: -2.0 to -3.0	1.06	0.96 – 1.17	0.223
FVC z-score: ≤ -3.0	1.17	1.03 – 1.33	0.011
Asbestos-Related Disease (ARD) Category			
[*] No ARD	-	-	-
ARD 1	1.16	1.05 – 1.27	0.002
ARD 2	1.14	0.96 – 1.35	0.127
ARD 3	2.88	1.84 – 4.51	0.000
ARD 4	2.52	2.12 – 2.99	0.000
Not determined	1.31	1.05 – 1.62	0.016
Time-varying Effects (Levels of covariates)			
Predictor	**Adjusted Hazard Ratio**	**95% CI**	**p-value**
BMI Category-Overweight	0.77	0.76 – 0.78	0.000
BMI Category-Obese	0.78	0.77 – 0.79	0.000
FEV z-score ≤ -3.0	0.78	0.77 – 0.80	0.000
Time-varying Effects (Entire covariates)			
Predictor	**Adjusted Hazard Ratio**	**95% CI**	**p-value**
Diffuse Pleural Thickening	1.00	0.98 – 1.02	0.867
[*]Reference category			

Table SIV: Results of interaction term between ILO profusion category and smoking status modelled in a Cox regression			
Category	**Adjusted Hazard ratio**	**95 % CI**	**p-value**
Smoker and ILO Profusion category 1	0.95	0.83 – 1.09	0.467
Smoker and ILO Profusion category 2 (n=46)	1.32	0.87 – 1.99	0.192
Smoker and ILO Profusion category 3 (n=12)	1.39	0.60 – 3.25	0.446
* Reference category is non-smokers with no radiological evidence of asbestosis (ILO profusion category 0)			

Table SV: Median FEV_1 and FVC z-scores and raw median FEV_1 and FVC values across the main ILO profusion categories					
	ILO Profusion Category				
Spirometry	***Category 0**	**Category 1**	**Category 2**	**Category 3**	**p-value**
Median FEV_1 z-score	-1.227 (IQR:-2.072; -0.401)	-1.660 (IQR:-2.405; -0.789)	-2.111 (IQR:-2.967; -1.139)	-1.872 (IQR:-2.775; -1.274)	0.002
Median FVC z-score	-1.223 (IQR:-2.034; -0.258)	-1.613 (IQR:-2.569; -0.592)	-2.108 (IQR: -3.072; -1.061)	-2.078 (IQR: -2.923; -0.851)	<0.000
Raw Median FEV_1 (litres)	2.45 (IQR: 1.95; 2.95)	2.24 (IQR: 1.77; 2.70)	1.82 (IQR: 1.52; 2.21)	1.72 (IQR: 1.61; 2.07)	0.000
Raw Median FVC (litres)	3.16 (IQR: 2.55; 3.77)	2.93 (IQR: 2.34; 3.52)	2.49 (IQR: 2.02; 2.96)	2.36 (IQR: 1.84; 2.82)	0.000

* Reference category

FEV_1 Normal: FEV_1 z-score :≥ -1.64
FEV_1 Low: FEV_1 z-score: < -1.64
Mild: FEV_1 z-score: < -1.64 but > -2.0
Moderate: FEV_1 z-score: ≤ -2.0 but > -3.0
Severe: FEV_1 z-score: ≤ -3.0

FVC Normal: FVC z-score: ≥ -1.64
FVC Low: FVC z-score: < -1.64
Mild: FVC z-score: < -1.64 but > -2.0
Moderate: FVC z-score: ≤ -2.0 but > -3.0
Severe: FVC z-score: ≤ -3.0

Table SVI: Frequency of asbestos-related disease across nature of work categories in females (N=1955) and males (N=9388)

Females (N=1955)							
Nature of Work	**ARD Category n (%)**						
	ARD 0	**ARD 1**	**ARD 2**	**ARD 3**	**ARD 4**	**ARD 5**	**p-value**
*Belowground	18 (0.9%)	10 (0.5%)	5 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.000
Aboveground	1405 (71.9%)	355 (18.1%)	37 (1.9%)	5 (0.3%)	48 (2.5%)	33 (1.7%)	
Unspecified	27 (1.4%)	11 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.05%)	0 (0.0%)	
Total	1450 (74.1%)	376 (19.2%)	42 (2.1%)	5 (0.3%)	49 (2.5%)	33 (1.7%)	
Males (N=9388)							
Nature of Work	**ARD Category n (%)**						
	ARD 0	**ARD 1**	**ARD 2**	**ARD 3**	**ARD 4**	**ARD 5**	**p-value**
*Belowground	1124 (12.0%)	1113 (11.9%)	126 (1.3%)	15 (0.2%)	35 (0.4%)	60 (0.6%)	0.000
Aboveground	4516 (48.1%)	1669 (18.1%)	193 (2.1%)	22 (0.2%)	162 (1.7%)	117 (1.2%)	
Unspecified	64 (0.7%)	96 (1.0%)	16 (0.2%)	2 (0.02%)	17 (0.2%)	11 (0.1%)	
Total	5704 (60.8%)	2908 (31.0%)	335 (3.6%)	39 (0.4%)	214 (2.3%)	188 (2.0%)	

*Reference category

No ARD
Spirometry: FEV1 and FVC ≥ 80%
FEV1/FVC ratio ≥ 75%
Radiological: No evidence of asbestosis/asbestos-related changes

ARD 1
Asbestos-related pleural thickening/asbestosis with mild to moderate lung function impairment
Spirometry: FEV1 and FVC ≥ 52% but < 80%
FEV1/FVC ratio ≥ 55% but < 75%
Radiological: ILO reading consistent with asbestosis/asbestos- related changes

ARD 2
Asbestos-related pleural thickening/asbestosis with severe lung function impairment
Spirometry: FEV1 and FVC < 52%
FEV1/FVC ratio < 55%
Radiological: ILO reading consistent with asbestosis/asbestos- related changes

ARD 3
Asbestos-related Lung cancer
Based on histological evidence

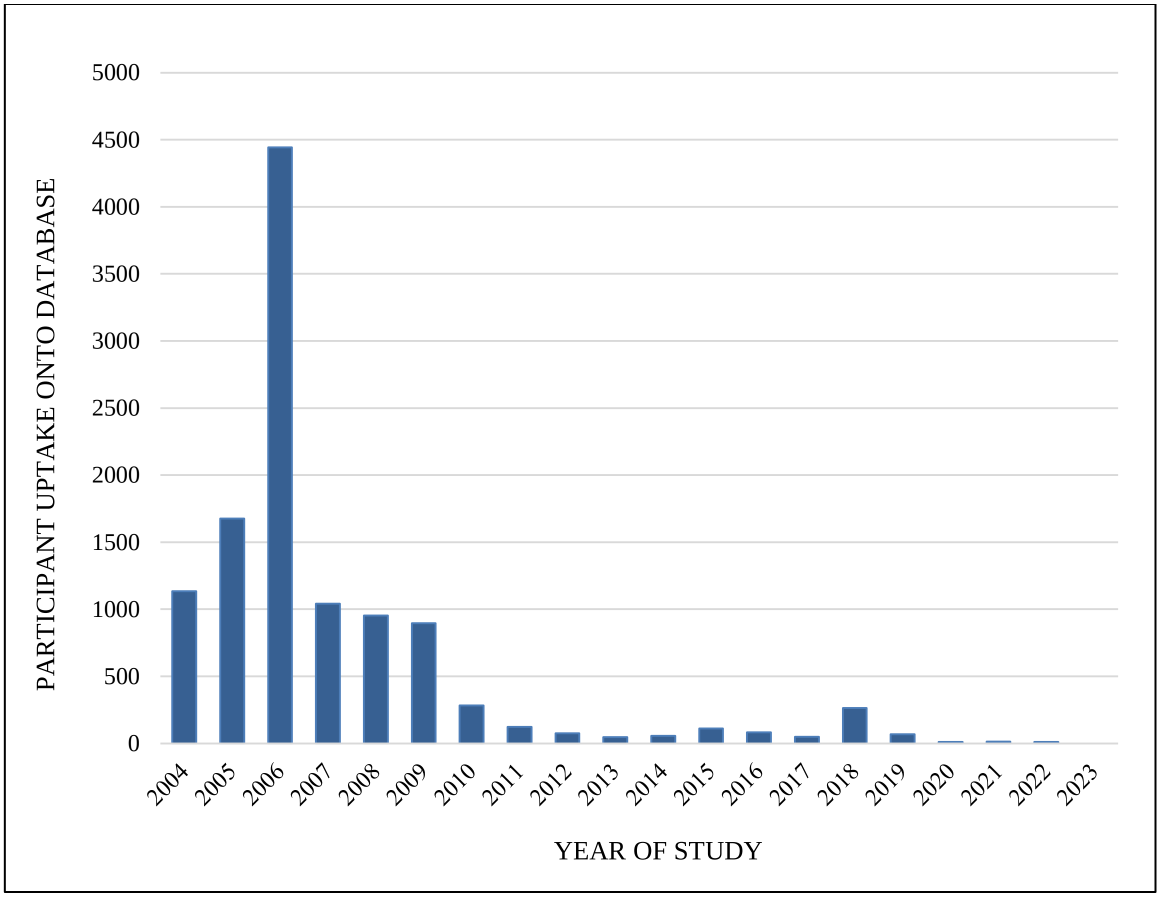
ARD 4
Mesothelioma
Based on histological evidence

ARD 5
Category not determined yet

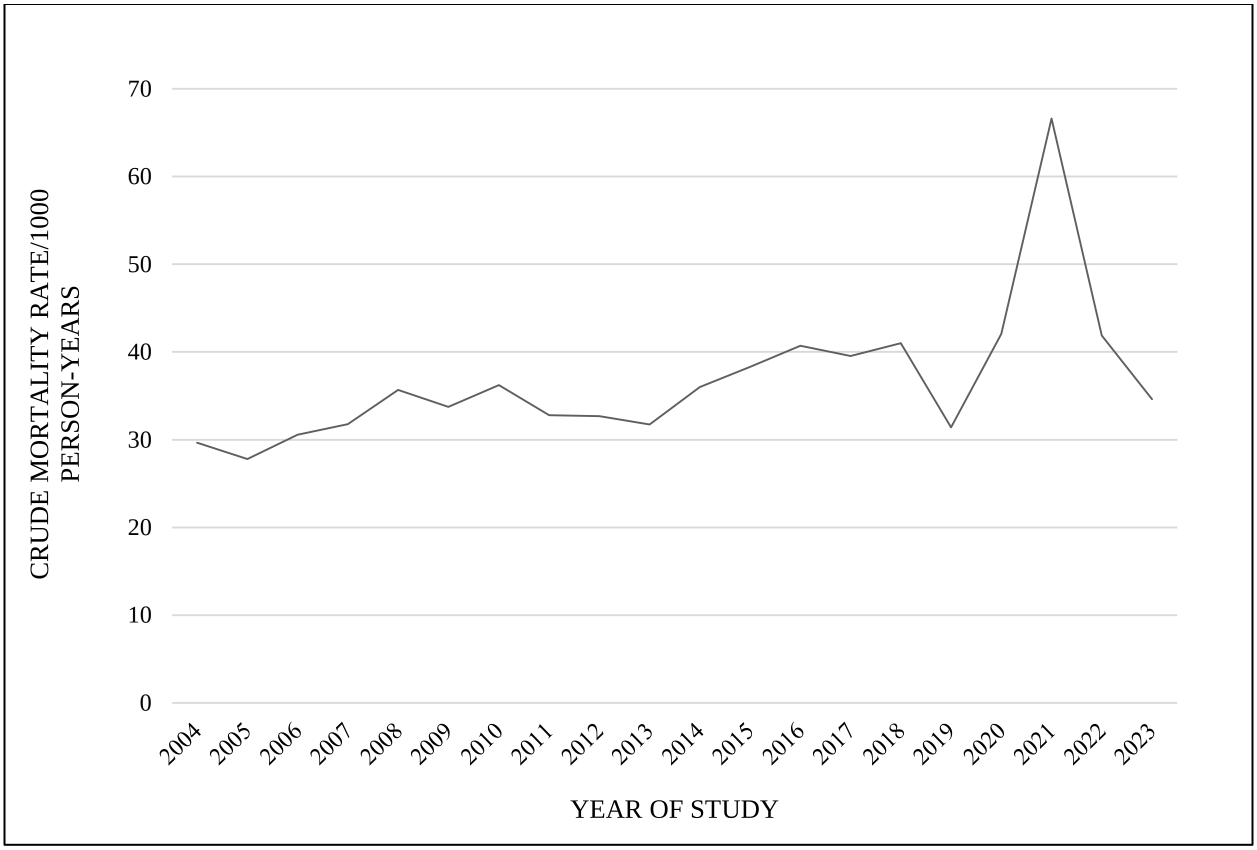
Table SVII: Type of asbestos exposure across nature of work categories in females (N=1955) and males (N=9388)

Nature of work	Type of asbestos exposure n (%)					
Females (N=1955)						
	Chrysotile	Crocidolite	Amosite	Mixed	Unspecified	p-value
*Belowground	8 (0.4%)	10 (0.5%)	6 (0.3%)	0 (0.0%)	9 (0.5%)	0.000
Aboveground	114 (5.8%)	678 (34.7%)	12 (0.6%)	6 (0.3%)	1073 (54.9%)	
Unspecified	1 (0.05%)	11 (0.6%)	0 (0.0%)	0 (0.0%)	27 (1.4%)	
Total	123 (6.3%)	699 (35.8%)	18 (0.9%)	6 (0.3%)	1109 (56.7%)	
Males (N=9388)						
*Belowground	822 (8.8%)	1210 (12.9%)	58 (0.6%)	35 (0.4%)	348 (3.7%)	0.000
Aboveground	1350 (14.4%)	2871 (30.6%)	202 (2.2%)	39 (0.4%)	2247 (24.0%)	
Unspecified	43 (0.5%)	112 (1.2%)	0 (0.0%)	1 (0.01%)	50 (0.5%)	
Total	2215 (23.6%)	4193 (44.7%)	260 (2.8%)	75 (0.8%)	2645 (28.3%)	

*Reference category



<u>Figure S1</u>: Participant uptake onto the Asbestos and Kgalagadi Relief Trust database over the 20-year study period



<u>Figure S2</u>: Crude mortality rate among Asbestos and Kgalagadi Relief trust claimants for each year of the study period from 2004 to 2023

Figure S3: Fitted regression line determining the average increase in crude mortality per annum for the duration of the study

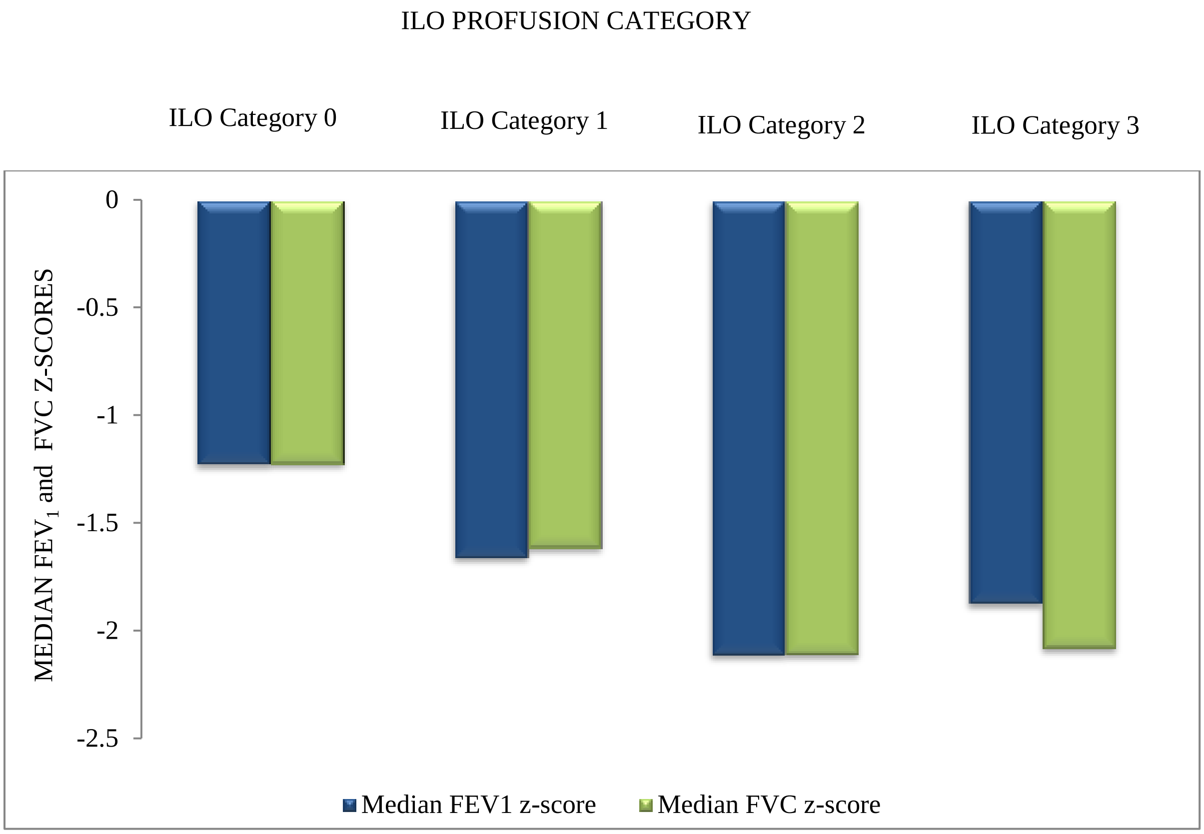


Figure S4: Median FEV_1 and FVC z-scores across the main ILO profusion categories

Appendix 8: Journal Instructions and Guidelines for the Authors

American Journal of Industrial Medicine – Author Guidelines

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3. Centers for Disease Control and Prevention (CDC). Licensure of a meningococcal conjugate vaccine (Menveo) and guidance for use--Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Morb Mortal Wkly Rep. 2010;59(9):273.

Electronic Journal article: If you have a doi (preferred):

4. Gage BF, Fihn SD, White RH. Management and dosing of warfarin therapy. Am J Med. 2000;109(6):481-488. https://doi.org/10.1016/S0002-9343(00)00545-3.

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5. Aggleton JP. Understanding anterograde amnesia: disconnections and hidden lesions. Q J Exp Psychol. 2008;61(10):1441-1471. http://search.ebscohost.com/login.aspx?direct=true&db=pbh&AN=34168185&site=ehost-live. Accessed March 18, 2010.

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6. Chau NG, Haddad RI. Antiangiogenic agents in head and neck squamous cell carcinoma: tired of going solo [published online ahead of print September 20, 2016]. Cancer. https://doi.org/10.1002/cncr.30352.

Entire Book:

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Book Chapter:

8. Guyton JL, Crockarell JR. Fractures of acetabulum and pelvis. In: Canale ST, ed. Campbell's Operative Orthopaedics. 10th ed. Philadelphia, PA: Mosby, Inc; 2003:2939-2984.

Electronic Book:

9. Rudolph CD, Rudolph AM. Rudolph's Pediatrics. 21st ed. New York, NY: McGraw-Hill Companies; 2002.http://online.statref.com/Document/Document.aspx?DocID=1&StartDoc=1&EndDoc=1882&FxID=13&offset=7&SessionId=A3F279FQVVFXFSXQ . Accessed August 22, 2007.

Internet Document:

10. American Cancer Society. Cancer Facts & Figures 2003. http://www.cancer.org/downloads/STT/CAFF2003PWSecured.pdf. Accessed March 3, 2003.

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