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Dlamini, Wendy Wandile

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THE ASSOCIATION BETWEEN MANGANESE EXPOSURE, PARKINSONISM, AND QUALITY OF LIFE IN SOUTH AFRICAN MANGANESE MINE WORKERS

WENDY WANDILE DLAMINI (1064883)

School of Public Health



Supervisor: Professor Gill Nelson, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Co-Supervisor: Professor Brad Racette, Department of Neurology, Washington University School of Medicine, St. Louis, United States of America

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FEBRUARY 2018

DECLARATION

I, Wendy Wandile Dlamini, hereby declare that the research project entitled "*The Association between Manganese Exposure, Parkinsonism and Quality of Life in South African Manganese Mine Workers*" is a record of bonafide work undertaken by me under the supervision of Professors Gill Nelson and Brad Racette. It is submitted in partial fulfillment of the requirements for the degree of Master of Science in Epidemiology and Biostatistics in the School of Public Health, University of the Witwatersrand. All sources quoted in this project have been appropriately cited. This work has not been submitted previously to any other institution for the award of any degree.



Wendy Wandile Dlamini

20 February 2018

DEDICATION

This project is dedicated to my mother, Victoria Zodwa Nyawo. Thank you for your encouragement, your prayers, your faith in God and in me, and for your unrelenting support throughout this adventure. Finally, thank you for your selfless love. I love you, Dumakude.

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Some final thanks go to my mother, VZ Nyawo, my siblings (Anele and Notsile), and to my numerous friends who endured this long process with me, always offering love and support. To Thandiwe N Mthiyane, Brenda A Oulo, and Nozipho S Mkhathswa, thank you for your contributions and for accepting nothing less than excellence from me.

Over and above: Glory, Honor and Praise be unto God.

ABSTRACT

Background

Manganese is an essential micronutrient for humans, but excessive levels are harmful. Manganese neurotoxicity is associated with parkinsonism and the associated motor deficits can affect an individual's daily activities and quality of life (QoL) in manganese–exposed persons.

Objectives

In this study, we sought to investigate the associations between manganese, parkinsonism and QoL in South African manganese mine workers, in the period 2010–2014.

Methods

This was a secondary analysis of data from 418 South African manganese mine workers already recruited into a prospective study of the association between Mn mining exposure and parkinsonism. Parkinsonism, the primary outcome, was defined as a Unified Parkinson's Disease Rating Scale motor subsection part 3 score (UPDRS-3) ≥15. The 39–item Parkinson's Disease Questionnaire (PDQ-39) was used to assess miners' health status or QoL, the secondary outcome. Cumulative manganese exposure in mg/m^3-year (measured as inhalable dust) was estimated using an exposure matrix from participants' job histories. We used Mann-Whitney and Pearson's Chi-Square tests to compare participants' parkinsonism status with regard to baseline continuous and categorical characteristics. Multiple linear and logistic regression modeling was used to quantify associations.

Results

The mean age of the manganese mine workers was 41.5 years (SD=11.9); 97.6% were male. Average manganese exposure was estimated as 3.7 mg/m^3-years (SD=5.8) at baseline with mean duration of 13.5 years (SD=11.7). The prevalence of parkinsonism was 29.4%. Participants' characteristics, stratified by parkinsonism status, differed significantly by age, education, and comorbid disease. Parkinsonism prevalence decreased significantly with increasing miners' education status, p=0.029 and was higher (36.4% vs 25.9%, p=0.042) in those with comorbidities. Parkinsonism participants were generally older (mean age 45.3 vs 39.6, p<0.0001). QoL sub-scores and total scaled PDQ-39 score means were higher in mine workers with parkinsonism compared to those without. We found no evidence of a monotonic dose-response relationship between cumulative manganese exposure and parkinsonism. Similarly, there was no statistically significant association between QoL and cumulative manganese exposure. Being aged 40 years or older was an independent risk factor for having parkinsonism (OR=2.11, 95% CI: 1.18, 3.78). Parkinsonism (β=0.63, p=0.004) and age (β= -0.48, p=0.031) were strong predictors of QoL.

Conclusion

We found a strong association between parkinsonism and QoL in manganese mine workers, confirming previous reports in manganese–exposed welders. There was no evidence of an association between parkinsonism and manganese exposure. The lack of a monotonic dose–response relationship between parkinsonism and manganese exposure may be due to the healthy worker survivor effect, a non-linear relationship, or exposure misclassification.

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ABBREVIATIONS

ADL	Activities of Daily Living
BMI	Body Mass Index
HEG	Homogeneous Exposure Group
OEL	Occupational Exposure Limit
PD	Parkinson Disease
PDQ-39	39–item Parkinson Disease Questionnaire
QoL	Quality of Life
SF-36	36–item Short Form Health Survey
UPDRS-3	Unified Parkinson Disease Rating Scale motor subsection part 3

CHAPTER 1: INTRODUCTION

This chapter begins with a description of manganese, both as a trace element and a micronutrient, followed by an account of its neurotoxicity, how it links to parkinsonism, and a description of quality of life (QoL) in manganese–exposed individuals. The problem statement and justification of the study are described and the chapter concludes with the study aim, and objectives.

1.1 Background

Manganese is a trace element that is required throughout the life span of human beings. It is an abundant metal in the Earth's crust, usually occurring with iron, and is naturally present in soil, rocks, and certain foods. Manganese reserves are found primarily in China, Ukraine, Australia, South Africa, and Gabon. However, 80% of the world's manganese reserves are in South Africa (1-3). Manganese exists in both organic and inorganic forms. The main dietary sources of manganese (organic) include whole grains, nuts, tea, and green leaves (4-7). Primary industrial uses for inorganic manganese include i) additive in steel production and fuel oil, ii) an oxidant for bleaching, cleaning and disinfection, and iii) ingredient in various consumer products such as cosmetics, fireworks, and dry-cell batteries (8, 9).

Manganese is an essential biological nutrient for all living organisms, serving both enzymatic and structural functions (10, 11). It plays a role in regulating and/or binding to numerous enzymes in the body, acting as both an enzyme activator (e.g. decarboxylases) and a constituent element for a number of important enzymes (12).

For example, manganese is a co-factor for manganese superoxide dismutase which is a key enzyme in the prevention of oxidative damage; it is also a required element in the urea cycle (8, 9).

While manganese is essential for life, prolonged or excessive exposure is harmful to humans. High levels of exposure can occur in occupational settings and, over the last decade or so , there has been renewed interest in manganese toxicity in various work environments, given evidence of adverse health effects occurring at levels below regulatory thresholds (13). The potential for chronic exposure to high levels of manganese occurs specifically in workers exposed to welding fumes, manganese dust in manganese mines, and manganese smelter emissions (14).

The source of overexposure to manganese is both environmental and occupational (14). In the general population, exposure is commonly through diet, air inhalation, contaminated water or soil, and contact with manganese-contaminated surfaces (8). In occupational settings, manganese exposure is predominantly through inhalation (15), which several studies have suggested is the most harmful route (16, 17). Absorption of inhaled manganese into the central nervous system is reported to be 10 times greater than that absorbed orally (16, 17).

The primary target of manganese neurotoxicity is the central nervous system; although cardiac, liver, foetal, reproductive and lung toxicity have also been noted (12). At very high levels, initial manganese toxicity symptoms are subtle, and include poor sleep, mood changes, changes in appetite, fatigue, and behavioural changes (18). These are usually insidious and can be progressive.

Evidence suggests that insufficient intake of manganese impairs organ function, contributes to bone deformities, retards growth, and causes birth defects, amongst other ailments (11, 16, 19), whereas high levels of manganese are toxic and lead to detrimental health effects (8, 13, 20, 21). The most common adverse health outcomes associated with excess levels of manganese exposure are motor and cognitive dysfunction (14, 17, 22).

Classically, manganese neurotoxicity is associated with a severe movement disorder characterised by parkinsonism, dystonia, cognitive dysfunction, and behavioural disturbances (manganism) (23-25). Parkinsonism is a movement disorder characterised by the presence of two or more of the cardinal clinical signs of Parkinson Disease (PD): rigidity, bradykinesia, rest tremor or postural instability (26, 27).

Parkinsonism can result in significant motor deficits with loss of ambulation and independence. As the disease progresses, it is characterised by increasing motor disability and impairment, eventually affecting an individual's daily activities and his/her expected or usual physical, mental and social health, referred to as health-related (28, 29). For instance, problems with movement can lead to limitations in performing self-care activities, depression, social seclusion, etc. In the workplace, poor health outcomes linked to exposure to manganese can affect job performance and worker safety. This could be in the form of decreased productivity, associated work absenteeism, job stress, and increased risk of occupational injuries (30).

1.2 Literature Review

1.2.1 Manganese Toxicity

It has long been established that the micronutrient, manganese, is also a neurotoxic substance (18). Occupational exposure, in particular, has been reported to cause manganese toxicity (31). Neurotoxicity results from the accumulation of manganese in the brain tissue (12). Several factors are associated with manganese toxic effects, including the duration, dose, and route of manganese exposure.

In a blinded control study published in 1996 (32), assessing motor deficits in manganese-exposed persons, 27 Chilean miners exposed to manganese for more than five years, and 32 controls, were examined and compared. The manganese-exposed cohort was observed to frequently exhibit more action and resting tremor, and general difficulties in motor function than the control group. Subclinical changes in motor impairment were also noted in the miners. The authors concluded that chronic exposure to manganese in this cohort of asymptomatic miners resulted in detectable late-life movement abnormalities. Guilarte, in a 2013 review, reported that manganese intoxication produces motor dysfunction and cognitive deficits in both human (23) and non-human subjects (33). In another study of a cohort of male smelter workers, published in 2015, poorer lung function was associated with cumulative exposure to manganese–containing dust (34).

1.2.2 Low and High Levels of Manganese

Mergler and Baldwin, reported that studies on early neurofunctional changes associated with manganese in the workplace collectively showed a significantly higher prevalence of hand unsteadiness and altered motor function at exposure levels below 5 mg/m^3 of total manganese dust (14). Effects of low exposure levels of manganese (approximately 0.2 mg/m^3) on the CNS were investigated in 138 manganese-exposed enamel production workers and 137 matched controls. No significant adverse effects on the nervous system function were reported. Subtle clinical symptoms such as headaches, weakness and sleep disturbances, instead, were noted (6, 35). An epidemiological study comparing male subjects working in a manganese plant to matched controls noted that the prevalence of adverse health effects was higher among the exposed group than the controls (36). These health effects were related primarily to the CNS, and lungs. The study demonstrated that time-weighted average exposure to manganese of about 1 mg/m^3 may still lead to the occurrence of preclinical adverse effects in some workers exposed for a period of less than 20 years. Cited among neurological signs in workers occupationally exposed to low manganese levels (0.07 to 0.97 mg/m3) were: lower cognitive flexibility levels, poorer hand steadiness, postural stability, and prolonged reaction time (8).

Inconsistent findings, however, have been reported in two major South African studies cross-sectionally investigating manganese associated nervous system effects in persons occupationally exposed. These concluded that persons exposed within the exposure ranges studied were unlikely to have a subclinical neurotoxicity problem. The associations observed were more likely to be due to chance.

In the one analysis, 489 blue and white-collar manganese mine workers exposed to an average 0.21 mg/m^3 of inhalable manganese dust were studied (37). In the other study, 509 production workers at a manganese smelter and 67 external controls were equally investigated. Average intensity exposure levels ranged from near 0 (0.06 mg/m^3) for external controls to 5.08 mg/m^3 for inhalable manganese dust in the latter study (38).

Manganese intoxication, as manganism was also noted from epidemiological studies conducted in occupational groups (such as manganese miners and steel manufacturing workers) chronically exposed to high levels of manganese. These cases of clinical neurotoxicity were typically observed in workers exposed to levels higher than 5 mg/m^3 (6). The United States Agency for Toxic Substances and Disease Registry (ATSDR) documented that workplace associated exposure levels ranging from about 2 to 22 mg/m^3, can result in acute, and potentially disabling, neurological effects (8).

1.2.3 Manganese Neurotoxicity and Parkinsonism

Reports on parkinsonism related to manganese exposure have focused on manganese neurotoxicity and welding as potential risk factors. Chronic inhalation of high levels of manganese, especially in occupational settings, has been linked to a syndrome comprising neuropsychological disturbances, parkinsonism and cognitive deficits (33). Occupational manganese-induced parkinsonism will sometimes manifest as manganism, a degenerative neurologic syndrome (25).

A recent (2016) study investigating the progression of parkinsonism was carried out in 886 welders with a mean duration of exposure to manganese of 4.2 years (24). This longitudinal analysis revealed Mn-dose dependent progressive parkinsonism. Prolonged manganese exposure also produces gradual psychological symptoms such as hallucinations, sleep disturbances, mood changes, psychosis, euphoria, and aggressiveness (33).

1.2.4 Quality of Life (QoL)

Neurotoxicity from occupational exposure to manganese from welding has been shown to be associated with parkinsonism, and the resulting motor deficits can affect an individual's daily activities and QoL (30). Manganese neurotoxicity can be a contributing factor to the slow deterioration of an individual's health status or QoL over time. That is, health might progressively deteriorate with increasing manganese exposure. The association between neurologic impairments and changes in worker health status has been investigated in only a few studies.

Standardised tools can be employed to determine the general well-being of subjects (30). The 39-item Parkinson Disease Questionnaire **(PDQ-39)** is one such health status questionnaire commonly used to assess the effect of parkinsonism on health status or QoL (30). It comprises 39 questions measuring eight QoL dimensions: mobility, activities of daily living (ADL), body discomfort, emotional well-being, social support, stigma, communication, and cognition (28, 39). All questions have five scoring options '0 to 4' (a likert scale), corresponding to 'never', 'occasionally', 'sometimes', 'often', and 'always/cannot do at all'.

The 36-item Short Form Health Survey **(SF-36)** is another commonly used tool to assess peoples' health status (40). The SF-36 tool can be applied to varied areas (clinical practice, research, general population surveys), and for patients suffering from different diseases. It is composed of 36 items corresponding to eight dimensions of health: mental health, vitality, general health, role-physical, bodily pain, social function, physical functioning, and role-emotional. Higher values in the SF-36 questionnaire indicate better health status.

Harris (2011), showed that welders with parkinsonism had poorer QoL or health status than those without parkinsonism across all QoL dimension sub-scores (30). In this study, the PDQ-39 was administered to examine the effects of parkinsonism on health status in welding–exposed workers. Another study conducted in Shanghai, China (2014) used the 36-item Short Form Health Survey (SF-36) to assess QoL in 301 male welders and 305 non-dust exposed male workers (40). The SF-36 health status dimensions were significantly worse in the welders than in the controls. A more recent (2015) study in 275 Ohio residents reported that air manganese concentrations were significantly associated with poor mental health and poor physical health, suggesting that environmental manganese exposure may also adversely affect QoL (41).

1.3 Problem Statement

Numerous authors have documented that neurotoxicity as a result of high or prolonged manganese exposure is a concern in some occupational settings. Manganese exposure occurs mainly during the mining and the smelting of ore (42), but there have also been reports of manganese exposure in welders.

Exposure to manganese has been associated with motor dysfunction, including chronic and progressive parkinsonism, as well as poor health status. However, epidemiological evidence to quantify these findings in manganese mining and smelting is limited.

Generally, Africa's contribution to neuroscience research is limited (43). Although parkinsonism is a common health problem globally, little is known about its prevalence or epidemiology in Africa. Most research on the health effects of manganese has established that excess manganese exposure can result in clinical and/or subclinical neurologic impairments, disability, and/or diminishing QoL (44, 45). These issues have received little attention in Africa, and even globally, there is limited research evaluating the chronic effects of low levels of manganese exposure.

In addition, the threshold level for manganese exposure has not been tested with regard to adverse health effects (6, 8). Although policies exist in some countries (including South Africa) to regulate manganese exposure in occupational settings, reports of manganese neurotoxicity continue (12). The existing occupational exposure limit (OEL) on manganese dust and compounds (5 mg/m^3) published in the 1995 South African Regulations for Hazardous Chemical Substances was last updated in 2008 and might, therefore, be out of date and no longer applicable (46). An OEL is the level to which workers are exposed during their working career that should not cause any adverse health effects to them or their offspring (46).

1.4 Justification

The health effects of manganese exposure in the modern mining sector is under–researched. This study presents an opportunity to expand on the neurological research gap in the African context. South Africa accounts for more than 80% of the world's known manganese resources, occurring predominately in the Northern Cape Province (1, 47), providing a good setting for the study. In 2016, the South African manganese mining industry employed around 7 000 workers (48). Given the potentially serious consequences of high or prolonged exposure to manganese, viz., chronic neurologic disorders, it is important to better understand the relationships between manganese exposure, neurological effects, and QoL in manganese mine workers in South Africa.

Demonstrating the associations between manganese exposure, parkinsonism and QoL may have important occupational, legislative, social and clinical implications, and could have significant repercussions for worker safety and performance (30).

The threshold exposure level of manganese for the development of neurobehavioural or subclinical neurological effects has not been established (6). As such, this research sought to advance new knowledge to provide guidance for regulating OELs in manganese mining and enhancing health prevention strategies.

1.5 Study Aim

The aim of the study was to investigate the association between manganese exposure, parkinsonism, and quality of life in manganese–exposed mine workers in South Africa.

1.6 Objectives

1. To estimate the prevalence of parkinsonism in a cohort of manganese-exposed mine workers in South Africa.
2. To describe quality of life in those mine workers with and without parkinsonism.
3. To determine the association between manganese exposure and parkinsonism among the manganese mine workers.
4. To determine the association between manganese exposure and quality of life among the manganese mine workers.

CHAPTER 2: METHODS

This chapter describes, in detail, the methods used in the analysis of the data, and includes a description of the study design, study site, study population, power calculations, the study variables and their measurement, and data management and analyses. Ethical considerations for this study are also addressed.

2.1 Primary Study Methodology

A prospective cohort study was implemented in 2010, comprising 418 manganese mine workers from four manganese mine shafts and an open pit located in the Northern Cape Province, South Africa: Mamatwan (open pit); and Wessels, Gloria, Nchwaning 2 and Nchwaning 3 (underground). The aim of the study was to examine the association between manganese exposure and the signs and symptoms of parkinsonism. All active workers from the five worksites were eligible to participate in the study. The participating mine workers were followed up annually, for a period of five years.

Data were collected using three main data collection instruments: a) Unified Parkinson Disease Rating Scale motor subsection part 3 (**UPDRS-3)**, a valid and reliable clinical tool for assessing PD (49); b) **PD symptom questionnaire**, a short, but specific and sensitive tool for identifying individuals with symptoms of parkinsonism (50); and c) **PDQ-39 questionnaire** a health status and health–related QoL questionnaire – a self-administered, validated questionnaire with acceptable levels of test-retest and internal consistency reliability in PD respondents (39).

Additional data were extracted from employee annual medical examinations and human resources files. Participants' demographic, behavioural (smoking, alcohol use), clinical and job history information were also collected using a structured questionnaire.

2.2 Secondary Data Analysis Methodology

2.2.1 Study Design

This study used a cross-sectional study design in the analysis of 418 manganese mine worker characteristics at baseline exam, using the data prospectively collected in the primary study of parkinsonism in South African manganese miner workers, conducted in 2010-2014.

2.2.2 Study Site

Study participants were recruited from four manganese mine shafts and an open pit located in the Northern Cape Province, South Africa.

2.2.3 Effect Size

We computed the study's effect size using a two-sample proportions test. The significance level was set at 0.05. Given that the proportion of participants without parkinsonism was 0.71 and using a power of 0.80, the smallest detectable difference is –0.1308, with a corresponding proportion value of 0.58 [see Table 1].

Table 1: Computing effect size for a two–sample proportions test

Stata command: *"power twoproportions 0.71, test(chi2) power(0.8) n(418) direction(lower)"*	
Ho: p2 = p1 versus Ha: p2! = p1; p2 < p1	
Study parameters:	
alpha	0.0500
power	0.8000
N	418
N per group	209
p1	0.7100
Estimated effect size and experimental-group proportion:	
delta	-0.1308 (difference)
p2	0.5792

2.2.4 Study Variables and Measurement

Two outcomes were defined for the analysis:

1) Parkinsonism (binary variable): participants were diagnosed as having parkinsonism if the UPDRS-3 score was greater than or equal to 15 (≥15) (51). Parkinsonism was determined at any time point in the study during initial or follow-up examinations.
2) Quality of Life (continuous variable): the well-being of individuals was rated using the PDQ-39 questionnaire which was used to estimate a scaled QoL index score. The index score is a summarized standardized measure of the 8 QoL dimensions of the PDQ-39 questionnaire, such that a higher score indicates poorer QoL (52).

The exposure was cumulative manganese exposure (continuous variable), measured as inhalable dust, calculated from reported job titles which were then used to estimate mean exposures by homogeneous exposure group (HEG) and time.

The matrix estimate of cumulative exposure to manganese was calculated as:

$$CE_i = \sum C_g t_{ig}$$

where CE_i is the cumulative exposure for worker, i, and Cg is the arithmetic mean concentration for HEG, g and t_{ig} is the duration of work that worker i spent in HEG, g. This cumulative exposure matrix may also be adjusted to obtain exposures lagged for recent exposure (37), or in exploring specific etiologic hypotheses using exposure time windows.

An alternative measure of cumulative manganese exposure was 'duration of exposure in years' (continuous variable), defined as the total number of years worked in a manganese mine and calculated as the difference between job start and end dates in manganese mining. Both types of exposure measurements were included in the analysis.

Several additional, potentially confounding variables (demographic, clinical, and behavioural) were included in the analyses. These are described in detail in Table 2.

The following variables were analyzed as per the objectives:

For objective 1, parkinsonism was the outcome variable.

For objective 2, QoL was the outcome variable.

For Objective 3, parkinsonism was the outcome variable; and exposure variables were the cumulative exposure index and duration of exposure in manganese mining.

For Objective 4, the outcome variable was QoL; and exposure variables were parkinsonism, cumulative exposure index and duration of exposure in manganese mining.

Table 2: Potential confounding variables included in the analyses

#	Variable Name	Type	Description/Definition	Variable Coding
1	Age (years)	Continuous	Difference between participant's date of birth and study exam date, in years.	Actual value
2	Body Mass Index (BMI– kg/m^2)	Continuous	Weight-to-height ratio, calculated by dividing weight (kg) by the square of height (m).	Actual value
3	Sex	Categorical	Male or female.	1 = male 2 = female
4	Education	Categorical	Highest level of education attained, categorized into *no schooling* for uneducated study participants, *primary* for grades 1 – 7, and *secondary & above* for grades 8 – 12 and any further education e.g. vocational schools, college, university.	1 = no schooling 2 = primary 3 = secondary & above
5	Smoking	Categorical	Self-reported cigarette smoking status, classified as never smoked and ever smoked	0 = never-smoked 1 = ex-smoker 2 = current-smoker
6	Alcohol	Categorical	Self-reported alcohol use coded as either yes or no.	0 = no 1 = yes
7	Comorbidities	Categorical	Self-report of any other sickness or medical condition other than the outcome of interest (parkinsonism).	0 = no 1 = yes

In all models (i.e. objectives 3, 4) potential confounders included were socio-demographic factors (age, sex, and education), clinical characteristics (BMI and comorbidities), and behavioural variables (smoking status and alcohol use).

2.3 Data Management and Data Analysis

STATA version 13 statistical package (53) was used for data management and statistical analysis.

2.3.1 Data Management

The data management process involved extraction of the study-specific variables from the primary dataset. For exploratory data analysis, graphical display and frequency tables were used for a logical check for data inconsistencies. Duplicate entries were checked and deleted; validity checks were performed; incomplete and incorrect data were identified; and necessary modifications were made accordingly, e.g. data imputation. Data imputation involved replacing baseline missing data with available data from subsequent participant's visits. Some of the data were re-entered; and some variables were transformed, i.e. new variables were generated, some variable formats were changed, and other variables were recoded to meet the objective's data requirements.

2.3.2 Statistical Analysis

The estimated prevalence of parkinsonism among manganese mine workers was calculated as a proportion (objective 1). In addition, socio-demographic and other characteristics were compared for those with and without parkinsonism. Categorical variables were reported using frequencies (n) and proportions (%), whilst continuous variables were presented as mean (SD); differences were tested using the Mann-Whitney test for continuous variables, and Pearson's Chi-square test for categorical variables.

QoL was described and compared in those mine workers with and without parkinsonism (objective 2). Summary statistics for QoL were described using mean (SD) across all the eight QoL dimension sub-scores (mobility, ADL, stigma, emotional well-being, social support, cognition, communication, and body discomfort). The Mann-Whitney test was used to compare QoL sub-score means.

To determine the association between manganese exposure and parkinsonism the manganese mine workers (objective 3), parkinsonism was defined as a binary variable, “no and yes”. Predictors of parkinsonism were determined using a logistic regression model adjusted for probable confounders. Factors found to be significantly associated with parkinsonism using p-value less than 0.20 in the univariate analysis, were included in the multivariate logistic regression analysis. Manganese exposure (the main exposure variable) and the potential confounding variables, age, and smoking status, were included in the final model, regardless of their statistical significance.

We performed multiple linear regression analysis to determine the association between manganese exposure and QoL among the manganese mine workers (objective 4). Factors found to be significantly associated with QoL based on p-values less than 0.20 in the univariate analysis, were included in the multiple linear regression model, adjusting for probable confounders. Parkinsonism status (a variable of intrinsic interest), and age (a traditional confounder), were included in the final model, regardless of their statistical significance. The full multiple linear regression model was fitted, and residual diagnostics were performed to assess if model assumptions of normality and constant variance had been violated.

Normality plots were used to further assess normality of the QoL outcome variable. Violation of the constant variance assumption led to a transformation of the outcome variable. We computed margins to measure the effect of the fitted covariates (age, parkinsonism, and presence of comorbidities) on QoL. After estimating the margins, using the square root transformed data, we squared the estimates (back transformation) to report them in their original form. In addition, the variance inflation factor (VIF) was used to assess multi-collinearity in the fitted linear regression model, where a VIF with an average mean not considerably larger than 1 was preferred.

For the analyses regarding associations (objectives 3 and 4), the likelihood-ratio test was used in model selection. All final models were assessed for goodness of fit. A marginally significant p-value was defined as $0.05<p<0.10$. For all analyses, unless otherwise specified, a probability value of 0.05 was used to define statistical significance.

2.4 Ethical Considerations

Ethical clearance for both the primary prospective study and secondary analysis was granted by the University of the Witwatersrand Human Research Ethics Committee (clearance certificate numbers: M091038 and M1611110, respectively: Appendix B). To protect workers' confidentiality, we received unidentified data from the gatekeepers of the database. All computerised datasets were safeguarded with a password.

CHAPTER 3: RESULTS

A detailed narration of the findings of this study is presented in this chapter.

3.1 Selection of Study Participants for Analysis

Figure 1 depicts flow chart of exclusion criteria of the study sample

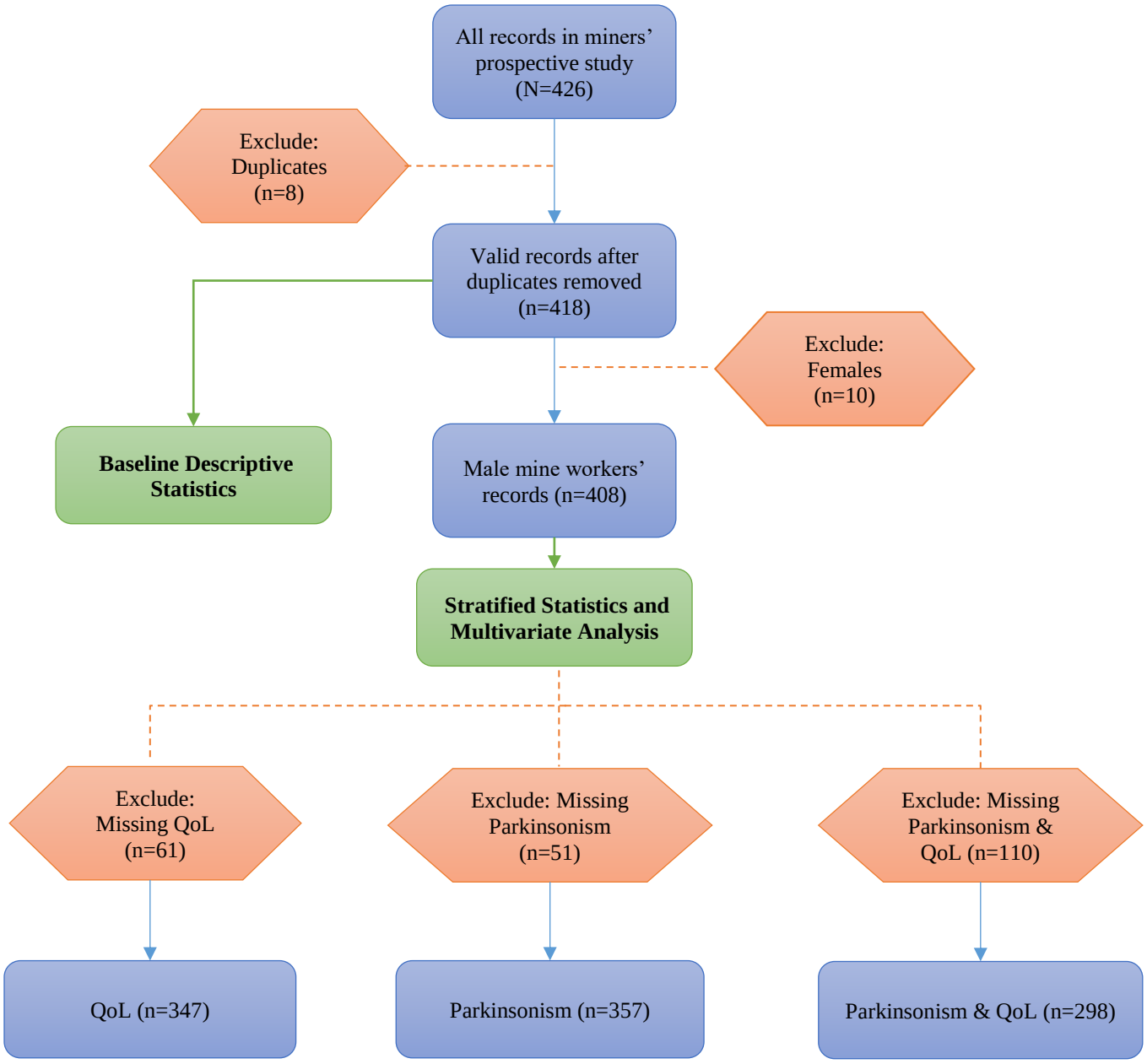


Figure 1: Exclusion process flow chart

A total of 426 participants were in the database of the manganese mine workers that was received from the gatekeepers. Eight participants were excluded because they were identified as duplicates, thus 418 mine workers remained in the database. Further, participants were excluded from analysis for the following reasons: small numbers which would result in spurious results and missing information for outcome variables (parkinsonism and QoL). A significant proportion of missing values of QoL might have resulted from respondents not completing the self-administered PDQ-39, health status questionnaire. Whereas, missing parkinsonism data might have been a result of the unavailability of a neurologist to perform a neurologic exam which includes the UPDRS-3, at any point during the time span of the study. Figure 1 illustrates the processes of exclusion, resulting in the following cluster sample sizes which were included in the final analysis: i) participants' baseline descriptive statistics (n=418); ii) parkinsonism data (n=357); iii) QoL data (n=347); and iv) parkinsonism and QoL data (n=298).

3.2 Description of Study Participants

Tables 3 and 4 display the socio–demographic, behavioural, and clinical characteristics of the 418 manganese mine workers. The mean age of the participants was 41.5 years (SD=11.9); 97.6% were male. More than half (57.4%) of the participants had attained secondary level education. Less than half (39.7%) reported that they drank alcohol, and 25.1% were current smokers. A third (33.7%) of the cohort reported having some physical ailment at their initial visit.

Table 3: Description of study participants (categorical variables, N=418)

Characteristic	n	%
Sex		
male	408	97.6
female	10	2.4
Age		
< 40	194	46.4
≥ 40	223	53.4
missing	1	0.2
Education		
no schooling	35	8.4
primary	88	21.1
secondary & above	240	57.4
missing	55	13.2
Smoking		
never-smoked	284	67.9
ex-smoker	23	5.5
current-smoker	105	25.1
missing	6	1.4
Alcohol Use		
no	239	57.2
yes	166	39.7
missing	13	3.1
Comorbidities		
no	262	62.7
yes	141	33.7
missing	15	3.6

As shown in Table 4, manganese mine workers had an estimated average of 3.7 mg/m^3-years (SD=5.8) of cumulative manganese exposure at baseline, and a mean duration of manganese exposure of 13.5 years (SD=11.7).

Table 4: Description of study participants (continuous variables, N=418)

Characteristic	mean	SD
Cumulative Mn exposure – mg/m^3-years	3.7	5.8
missing - n (%)	2	0.5
Duration of exposure – years	13.5	11.7
missing - n (%)	2	0.5
Age – years	41.5	11.9
missing - n (%)	1	0.2
BMI – kg/m^2	25.7	5.7
missing - n (%)	203	48.6

Mn: manganese

3.3 Prevalence of Parkinsonism in Manganese Mine Workers

The overall prevalence of parkinsonism (UPDRS-3 score ≥15) was 25.4%. Table 5 and Table 6, however, display participant's characteristics by parkinsonism status. In this stratification, female participants were excluded because of the very small number (n=10) [Table 3]. The resultant prevalence of parkinsonism in active male manganese workers was 29.4%.

There was an inverse, significant relationship between parkinsonism prevalence and miners' education status, i.e. a decreasing prevalence as education increased, p=0.029 [Table 5]. A higher prevalence of parkinsonism (36.4%) was noted among participants who reported comorbidities as opposed to 25.9% in those without comorbidities, p=0.042. Parkinsonism status did not differ significantly with respect to alcohol use (p=0.727) or smoking (p=0.451).

Table 5: Number and proportion of participants' characteristics by parkinsonism status

Variable		Parkinsonism n= 105		No Parkinsonism n= 252		Total N= 357	P-value
		n	**%**	**n**	**%**	**n**	
Sex							
	male	105	29.4	252	70.6	357	-
Age							
	< 40	35	20.5	136	79.5	171	
	≥ 40	69	37.3	116	62.7	185	**<0.0001***
	missing	1	100	0	0	1	
Education							
	no schooling	13	43.3	17	56.7	30	
	primary	27	36.5	47	63.5	74	
	secondary & above	52	24.5	160	75.5	212	**0.029***
	missing	13	31.7	28	68.3	41	
Smoking							
	never-smoked	66	27.5	174	72.5	240	
	ex-smoker	6	27.3	16	72.7	22	0.451
	current-smoker	32	34.4	61	65.6	93	
	missing	1	50	1	50	2	
Alcohol Use							
	no	57	28.2	145	71.8	202	
	yes	44	29.9	103	70.1	147	0.727
	missing	4	50	4	50	8	
Comorbidities							
	no	58	25.9	166	74.1	224	
	yes	44	36.4	77	63.6	121	**0.042***
	missing	3	25	9	75	12	

*p-values < 0.05 were considered statistically significant

Mean time-weighted cumulative manganese exposure among those with and without parkinsonism was 4.1 mg/m^3-years (SD=6.2) and 3.5 mg/m^3-years (SD=5.8), respectively [Table 6]. The mean age was 45.3 years (SD=12.8) for mine workers with parkinsonism and 39.6 years (SD=11.2) for those without.

Mean duration of exposure to manganese was significantly longer in mine workers with parkinsonism than in those without, 15 years (SD=12.0) and 12.9 years (SD=11.7), respectively.

Table 6: Description of participants' characteristics, by parkinsonism status

Variable	Parkinsonism		No Parkinsonism		Total		P-value
	n= 105		n= 252		N= 357		
	n	**mean (SD)**	**n**	**mean (SD)**	**n**	**mean (SD)**	
Cumulative Mn exposure – mg/m^3-years	105	4.1 (6.2)	251	3.5 (5.8)	356	3.6 (5.9)	0.1016
Duration of exposure – years	105	15.0 (12.0)	251	12.9 (11.7)	356	13.5 (11.8)	**0.0673***
Age – years	104	45.3 (12.8)	252	39.6 (11.2)	356	41.2 (11.9)	**0.0001***
BMI – kg/m^2	47	24.7 (4.6)	130	26.5 (5.7)	177	26.0 (5.5)	**0.0835***

*p-values < 0.05 were considered statistically significant; p-values 0.05<p<0.10 were considered marginally significant

Mn: manganese

3.4 Quality of Life in Manganese Mine Workers

Table 7 summarizes the PDQ-39 scores in participants with and without parkinsonism. All the mean QoL sub-scores, and the total mean PDQ-39 score, were higher in mine workers with parkinsonism than in those without. However, these differences between the two groups were statistically significant for only the mobility and, emotional well-being sub-scores, and PDQ-39 total score. The lowest sub-scores were noted for communication (4.5, SD=14.1) in mine workers with parkinsonism and stigma (2.6, SD=7.3) in those without parkinsonism. Other notable differences in scores between the two groups were for ADL and stigma, although these were not statistically significant.

Table 7: Quality of life/health status in manganese mine workers, by parkinsonism status

QoL DIMENSION	Parkinsonism		No Parkinsonism		Total		P-value
	n= 105		n= 252		N= 357		
	n	**mean (SD)**	**n**	**mean (SD)**	**n**	**mean (SD)**	
Total score	89	10.1 (13.0)	209	6.8 (8.4)	298	7.8 (10.1)	**0.0112***
Mobility	89	8.5 (15.8)	208	3.8 (8.6)	297	5.2 (11.4)	**0.0013***
ADL	89	6.1 (14.8)	208	2.7 (6.5)	297	3.7 (9.9)	0.1210
Emotional	88	16.7 (17.4)	208	12.6 (15.6)	296	13.8 (16.3)	**0.0427***
Stigma	88	5.7 (18.0)	207	2.6 (7.3)	295	3.5 (11.7)	0.3848
Social support	88	4.8 (13.5)	205	4.1 (12.3)	293	4.3 (12.6)	0.9749
Cognition	89	12.9 (16.2)	207	11.2 (16.9)	296	11.7 (16.7)	0.1789
Communication	89	4.5 (14.1)	204	3.8 (9.8)	293	4.0 (11.3)	0.7933
Body discomfort	89	23.8 (22.7)	204	19.2 (20.4)	293	20.6 (21.2)	0.1111

*p-values < 0.05 were considered statistically significant; ADL: activities of daily living

Females participants were excluded from this analysis due to the very small number (n=10). Likewise, BMI was excluded because it was missing in 48.6% of cases.

3.5 Association between Manganese Exposure and Parkinsonism

The results of the logistic regression analysis to ascertain the association between manganese exposure and parkinsonism are shown in Table 8.

Table 8: Association between manganese exposure and parkinsonism (logistic regression model)

Predictor Variable		Unadjusted OR	95% CI	P-value	Adjusted OR	95% CI	P-value
Cumulative Mn exposure – mg/m^3-years		1.02	0.98, 1.05	0.395	0.99	0.95, 1.03	0.648
Age							
	< 40	***reference***			***reference***		
	≥ 40	2.31	1.44, 3.72	**0.001***	2.11	1.18, 3.78	**0.012***
Smoking							
	never-smoked	***reference***			***reference***		
	ex-smoker	0.99	0.37, 2.63	0.982	0.85	0.29, 2.54	0.773
	current-smoker	1.38	0.83, 2.31	0.216	1.65	0.92, 2.94	**0.092***
Comorbidities							
	no	***reference***			***reference***		
	yes	1.64	1.02, 2.63	**0.043***	1.44	0.82, 2.53	0.201

OR: Odds Ratio; CI: Confidence Interval; Mn: manganese

*p-values < 0.05 were considered statistically significant; *p-values 0.05<p<0.10 were considered marginally significant

In both the unadjusted and adjusted analyses, cumulative manganese exposure in South African manganese mine workers' prospective study was not a significant predictor of parkinsonism.

Table 8 illustrates that age and comorbidities were individually, significantly associated with increased odds of parkinsonism. However, after adjusting for probable confounders; only age was a strong predictor of parkinsonism, whereas smoking status (current-smoker) was marginally significantly associated with parkinsonism.

The odds of parkinsonism in mine workers 40 years and/or older were 2.11 times (95% CI: 1.18, 3.78) the odds of parkinsonism in those younger than 40. The odds of parkinsonism in current smokers were 1.65 times (95% CI: 0.92, 2.94) the odds of parkinsonism in those who had never smoked.

We developed the same model using 'duration of exposure in years' as an alternative measure of manganese exposure. We found that duration of exposure was negatively associated with increased risk of parkinsonism (OR=0.97, 95% CI: 0.94, 1.00) [Appendix A, Table 11], contrary to earlier findings.

3.6 Association between Manganese Exposure and Quality of Life

Table 9 presents the summarized results from the multiple linear regression model built to evaluate manganese exposure as a predictor of QoL (measured using the square root of scaled PDQ-39 total score), adjusted for probable confounders.

Table 9: Association between manganese exposure and QoL (multiple linear regression model)

Predictor Variable		Unadjusted Model			Adjusted Model		
		β	**95% CI**	**P-value**	**β**	**95% CI**	**P-value**
Cumulative Mn exposure – mg/m^3-years		0.03	0.00, 0.06	**0.070***	0.02	-0.01, 0.05	0.201
Age							
	< 40	***reference***			***reference***		
	≥ 40	0.17	-0.21, 0.56	0.371	-0.48	-0.92, -0.05	**0.031***
Parkinsonism							
	no	***reference***			***reference***		
	yes	0.61	0.19, 1.03	**0.005***	0.63	0.20, 1.06	**0.004***
Comorbidities							
	no	***reference***			***reference***		
	yes	0.53	0.14, 0.91	**0.007***	0.42	-0.01, 0.84	**0.055***

QoL: measured using square root of total scaled PDQ-39 score; Mn: manganese

*p-values < 0.05 were considered statistically significant; *p-values 0.05<p<0.10 were considered marginally significant

In unadjusted analyses, parkinsonism (β=0.61, p=0.005) and comorbidities (β=0.53, p=0.007) strongly predicted increased QoL scores i.e. poorer QoL. Manganese exposure (β=0.03, p=0.070) was possibly associated with increased QoL scores.

After adjustment for socio-demographic, clinical and behavioural characteristics, parkinsonism (β=0.63, p=0.004) and age (β= -0.48, p=0.031) were strong predictors of a change in QoL score. Parkinsonism predicted poorer QoL and/or health status, and QoL was negatively associated with age. Manganese exposure did not significantly predict QoL, and the association between QoL and comorbidities was attenuated.

As summarized in Table 10, we used margins to measure the actual effect of age, parkinsonism, and comorbid disease on QoL.

Table 10: Margins estimates for QoL

Explanatory Variable		Margins estimate	95% CI	Back-transformed square root of total score	95% CI
Age					
	< 40	2.51	2.20, 2.83	6.32	4.82, 8.02
	≥ 40	2.03	1.76, 2.30	4.12	3.11, 5.27
Parkinsonism					
	no	2.05	1.82, 2.28	4.19	3.30, 5.18
	yes	2.68	2.32, 3.03	7.17	5.39, 9.21
Comorbidities					
	no	2.08	1.83, 2.33	4.31	3.33, 5.41
	yes	2.49	2.17, 2.82	6.21	4.69, 7.94

QoL: measured using square root of total scaled PDQ-39 score; CI: Confidence Interval

In this cohort, participants with parkinsonism and those who had reported any form of comorbid disease had significantly higher QoL scores relative to their referent groups (indicated by having no overlap in the 95% CI). On average, participants with parkinsonism had QoL scores that were 2.98 higher than those without. Similarly, the presence of any comorbid disease predicted a 1.90 higher QoL score relative to the 'healthy' participants.

The effect of age on QoL was evaluated by predicting QoL score estimates at several, specific values of age, as presented in Figure 2. We observed an inverse relationship between age and QoL i.e. QoL scores decreased (QoL improved) with increasing age. These results are consistent with the multiple linear regression model.

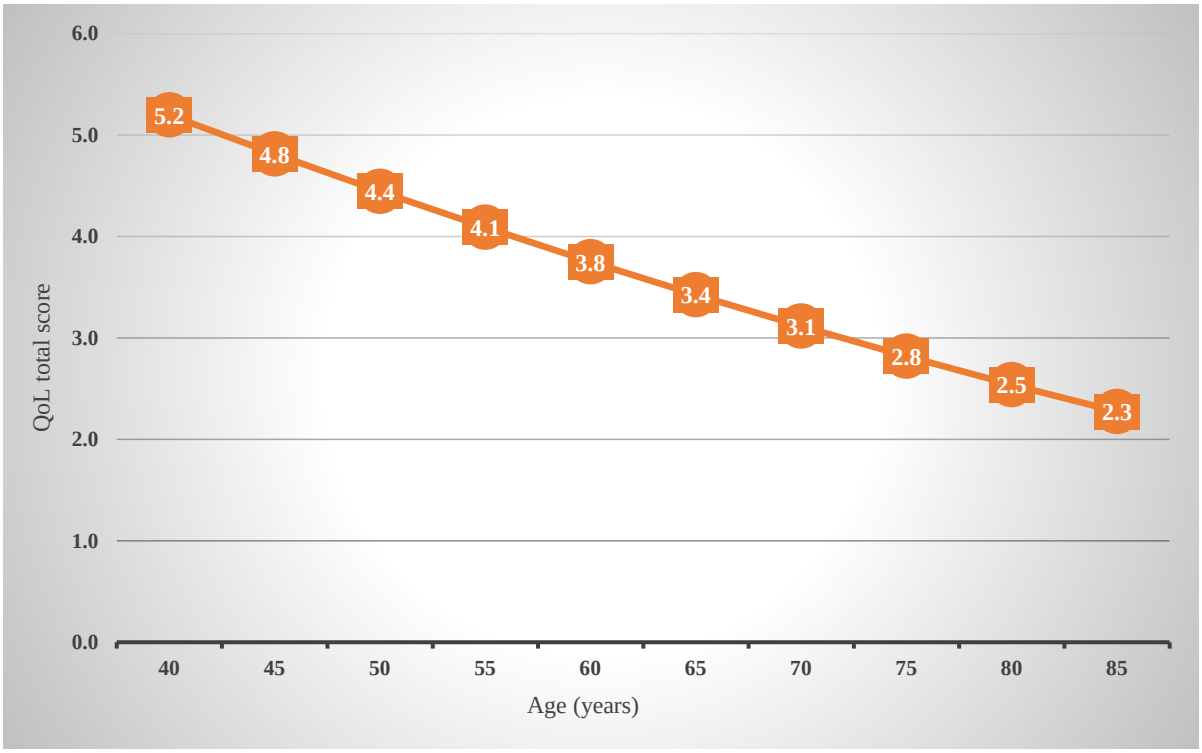


Figure 2: Predicted margins estimates quantifying the effect of age on QoL

We also performed multiple linear regression model with ‘duration of exposure in years’ as the primary exposure matrix [Appendix A, Table 12]. The findings of this analysis are consistent with our previous results, that is, parkinsonism and age were strong predictors of QoL.

CHAPTER 4: DISCUSSION

This chapter provides a detailed discussion on the study's findings, comparing these with what has already been published. It also outlines the study's strengths and limitations, and ends with the conclusion.

4.1 Synopsis of Study Findings

The aim of the study was to investigate the association between manganese exposure, parkinsonism, and quality of life in manganese-exposed mine workers in South Africa. There was an inverse, significant relationship between parkinsonism prevalence and miners' education status. Parkinsonism was a strong predictor of QoL. Cumulative manganese exposure, measured in mg/m^3-years, was not associated with either parkinsonism or QoL; whereas, duration of exposure in years, as an alternative measure of manganese exposure, was significantly associated with increased risk of parkinsonism. Age was a statistically significant predictor of both parkinsonism and QoL.

4.2 Prevalence of Parkinsonism in Manganese Mine Workers

The estimated prevalence of parkinsonism among the active male manganese workers was 29.4%. This was high compared to previously published research from two African nations: 3.7% (4/109) parkinsonism prevalence was reported in a neurology clinic in Ethiopia in 2005 (54) and a 16.7% (16/96) prevalence was reported in neurology out–patient clinics in Kano state, Nigeria in 2012 (26).

The latter study considered at least three of the four cardinal features of PD: bradykinesia, rigidity, tremors, and gait or postural abnormality in the diagnosis parkinsonism. Contrary to expectations, our occupational study had a higher prevalence of parkinsonism compared to these neurology patient-based studies. Differences in methodologies may explain this disparity.

The prevalence of parkinsonism was high compared to that reported in published studies from developed countries, e.g. Racette and co-workers reported prevalence rates of parkinsonism from two studies, 2016 and the other in 2012, of 15.2% and 15.6%, respectively, among welders occupationally exposed to manganese fumes (24, 51).

Parkinsonism rates have been reported as relatively low in Africa from several general population studies (29). Findings from this study reports a higher prevalence. This is a single study and is not representative of the general population, thus the results are not generalizable beyond manganese miners, but worth taking into consideration for future research and further investigations. Nevertheless, previously reported low rates, which are in contradiction to our findings, might suggest that parkinsonism is underdiagnosed in Africa, due to lack of expertise and limited resources, resulting in the low prevalence rates recorded. Another challenge in Africa is the dissemination of neuroscience research findings. Due to lack of funding and information access, most research is published in local journals (43) where it might not be accessed by international researchers. This could account for the disparities in the reported prevalence rates of parkinsonism as there is limited information internationally.

4.3 Quality of Life in South African Manganese Mine Workers with Parkinsonism

Similar to one previous occupational–epidemiological study (30), QoL sub-scores and PDQ-39 total score means were higher in workers with parkinsonism, relative to those without, confirming findings from other studies (30) that workers with parkinsonism tend to experience poorer health status than those without parkinsonism. This finding, coupled with the reported high prevalence of parkinsonism in our analysis, might have implications for early diagnosis, initiation to therapy and management of parkinsonism in the workplace to improve workers' QoL, or at least slow down the progressive deterioration of an individuals' health status.

The QoL scores for emotional well-being and mobility were significantly higher than the remaining QoL sub-domains. Motor deficits can limit the performance of individual's daily activities, whilst emotional instability can result in depression and other psychological and/or psychiatric disorders (28). Collectively or alone, these might affect job performance, increasing absenteeism, reducing productivity, and increasing the risk of injury in the workplace (30). This finding warrants further research on the neuropsychological impact of chronic exposure to manganese in healthy workers.

4.4 Association between Manganese Exposure and Parkinsonism

We found no evidence of a monotonic dose-response relationship between estimated cumulative manganese exposure and parkinsonism, despite the high prevalence of parkinsonism. Several epidemiological studies, mostly among welders, have evaluated the effects of manganese exposure in exposed individuals, and have found a significant association between occupational manganese exposure and parkinsonism (24, 45).

The lack of a monotonic dose–response relationship between parkinsonism and manganese mine exposure, in our analysis, may be due to the healthy worker survivor effect or a nonlinear relationship or that manganese levels were relatively low to induce parkinsonism. On average, manganese mine workers were exposed to an estimated 3.7 mg/m^3-years (SD=5.8) of cumulative manganese, with a median of 1.8 mg/m^3-years (IQR 0.7 – 3.6). Differing methodologies used in the diagnosis of parkinsonism and assessment of manganese exposure may also explain our findings. In the same analysis, duration of exposure was negatively associated with parkinsonism possibly due to a collinearity effect between duration of exposure and age.

The discordance in our findings emphasize the need for a consistent measurement approach of the manganese exposure matrix, to make research findings comparable across studies. Either 'duration of exposure' or the 'cumulative exposure matrix' is an inappropriate estimate of manganese exposure.

Being 40 years or older was most predictive of having parkinsonism. Several researchers have posited that older age is an important determinant of parkinsonism (26, 44). PD is very rare in individuals younger than 40 years (29, 55).

In some previous studies, smoking has been found to be protective against PD (negative association) (56, 57), yet we found a marginally significant positive association between smoking and parkinsonism in our study – suggesting that smoking might have no effect on parkinsonism induced by toxins, as opposed to induced PD and smoking.

4.5 Quality of Life Predictors

In this analysis, manganese exposure was not predictive of any change in individuals' QoL or health status in the manganese miners included in the primary prospective study. The association between manganese exposure and QoL has not been previously evaluated, but has rather been deduced from scientific reviews and reports on the neurotoxic symptoms that are usually displayed by chronically exposed individuals (58).

Increasing age was associated with improved QoL. This might be true of the general population, but contradicts plausible evidence of a negative association between age and QoL among PD patients (59, 60). This finding is surprising and to our best knowledge, this has not been previously reported. It is difficult to explain this finding, although the healthy worker effect is a possible reason for the inverse association between age and QoL.

We also found a strong association between parkinsonism and QoL. This supports Harris and colleagues' research where they reported elevated PDQ-39 total scores in parkinsonian welders compared to a referent group (30). Patients with parkinsonism frequently experience motor deficits which contribute to a decline in physical functional status, limiting work ability and performance of daily activities and impacting physical health and social interaction (28, 30). In the workplace, these, could have significant repercussions for worker safety and performance. Regression modelling using 'duration of exposure' or the 'cumulative exposure matrix' yielded the similar results, that is, parkinsonism and age were strong predictors of QoL.

4.6 Limitations

The prevalence of parkinsonism might be underestimated in this cohort due to the healthy worker survivor effect. Limitations with regard to the available information was expected, since data were not collected to answer the research question addressed in this report but, rather, were collected to determine if there was progression of parkinsonism in a cohort of manganese-exposed mine workers.

Although the primary study was conducted longitudinally, data were analyzed at baseline only due to missing data in subsequent visits. The cross-sectional nature of this study design means we are unable to infer causality, i.e. exposure and outcome were simultaneously assessed; thus, it is difficult to establish the temporal relationship between exposure and outcomes.

This study provides compelling evidence that parkinsonism in manganese miners is associated with abnormalities in QoL, but we cannot exclude the possibility that non-specific motor symptoms, not related to parkinsonism, might also be contributing to the QoL dysfunction.

We relied on an exposure matrix to indirectly estimate manganese exposure levels which potentially introduced exposure misclassification. The same matrix might be an inaccurate measure of manganese exposure in this group of mine workers, as it was developed in a different group. The matrix was computed using the mean rather than the median exposure; the median is an appropriate measure of central tendency for hygiene data because these are typically right skewed.

4.7 Strengths

Known confounders were considered by adjusting exposure effects using multivariate analysis. The use of (i) highly qualified personnel (e.g. movement disorders specialist) for clinical examination, thus disease misclassification unlikely and (ii) valid, specific, and reliable data collection instruments in the primary study, further strengthened this analysis.

4.8 Conclusion

The prevalence of parkinsonism in this group of mine workers was very high. Manganese mine workers with parkinsonism had poorer QoL or health status than those without parkinsonism. The results from the multivariate analysis, that parkinsonism strongly predicted QoL, corroborates this finding. These results support the hypothesis that parkinsonism in manganese–exposed workers is associated with poorer QoL, consistent with observations in other patients with parkinsonism.

Although an association between parkinsonism and manganese exposure was not demonstrated in this analysis, a parkinsonian syndrome associated with exposure to high levels of manganese has been previously described. Our finding does not preclude the possibility that chronic exposure to manganese, as occurs in mining, can lead to parkinsonism. South Africa's time-weighted average OEL for manganese dust and compounds is 5 mg/m^3. This threshold limit value has not been tested with regard to associated health effects in South Africa or the African region.

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APPENDIX A: Complementary Study Tables

Table 11: Association between duration of exposure and parkinsonism (logistic regression model)

Predictor Variable		Unadjusted OR	95% CI	P-value	Adjusted OR	95% CI	P-value
Duration of exposure – years		1.01	1.00, 1.03	0.133	0.97	0.94, 1.00	**0.041***
Age – years		1.04	1.02, 1.06	**<0.0001***	1.06	1.02, 1.09	**0.001***
Smoking							
	never-smoked	***reference***			***reference***		
	ex-smoker	0.99	0.37, 2.63	0.982	0.90	0.30, 2.65	0.844
	current-smoker	1.38	0.83, 2.31	0.216	1.65	0.92, 2.97	**0.094***
Comorbidities							
	no	***reference***			***reference***		
	yes	1.64	1.02, 2.63	**0.043***	1.48	0.82, 2.66	0.190

OR: Odds Ratio; CI: Confidence Interval; *p-values < 0.05 were considered statistically significant;

*p-values 0.05<p<0.10 were considered marginally significant

Table 12: Association between duration of exposure and QoL (multiple linear regression model)

Predictor Variable		Unadjusted Model			Adjusted Model		
		β	95% CI	P-value	β	95% CI	P-value
Duration of exposure – years		0.00	-0.01, 0.02	0.604	0.01	-0.01, 0.03	0.385
Age							
	< 40	***reference***			***reference***		
	≥ 40	0.17	-0.21, 0.56	0.371	-0.56	-1.10, -0.01	**0.045***
Parkinsonism							
	no	***reference***			***reference***		
	yes	0.61	0.19, 1.03	**0.005***	0.63	0.21, 1.06	**0.004***
Comorbidities							
	no	***reference***			***reference***		
	yes	0.53	0.14, 0.91	**0.007***	0.41	-0.02, 0.84	0.063

QoL: measured using square root of total scaled PDQ-39 score; *p-values < 0.05 were considered statistically significant;

*p-values 0.05<p<0.10 were considered marginally significant

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APPENDIX B: Plagiarism Declaration Form

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I **WENDY WANDILE DLAMINI** (Student number: **1064883**) am a student registered for the degree of **MASTER OF SCIENCE IN EPIDEMIOLOGY** in the academic year **2017**.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

Signature:  Date: **07 SEPTEMBER 2017**

APPENDIX C: Human Research Ethics Clearance Certificate

R14/49 Miss Wendy Wandile Dlamini

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M1611110

NAME: (Principal Investigator)	Miss Wendy Wandile Dlamini
DEPARTMENT:	Epidemiology and Biostatistics School of Public Health
PROJECT TITLE:	The Association between Manganese Exposure, Parkinsonism and Quality of Life in South African Manganese Mine Workers
DATE CONSIDERED:	25/11/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Gill Nelson
APPROVED BY:	Prof C Feldman, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	14/12/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in November and will therefore be due in the month of November each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date **06/02/2017**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES