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2022
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The effect of exposure to environmental manganese on the neurobehavioural function of children in Meyerton, South Africa

Annemarie McGovan

A dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand Johannesburg, in fulfilment of the requirements for the degree of Master of Science (Med) in Exposure Science**.**

Johannesburg, 2022

DECLARATION

I, Annemarie McGovan, declare that this dissertation is my own, unaided work. It is being submitted for the Degree of Master of Science (Med) in Exposure Science at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.



Annemarie McGovan

21 June 2022

ABSTRACT

Background

Manganese (Mn) is a heavy metal that occurs naturally. Humans are exposed to Mn from a variety of sources. The health effects of environmental exposure to Mn at lower than occupational exposure levels have been the focus of recent research in adults, but only a few studies have investigated the effects in children. No studies in children have been conducted in South Africa where 80% of the world's Mn reserves are located.

Objective

The objective of this research was to investigate the association between exposure to low levels of ambient Mn and neurodevelopmental outcomes, viz. cognitive- and motor-development, in children living and being schooled near a ferro-manganese smelter in the Midvaal area in Gauteng province, South Africa.

Methods

In this cross-sectional study, 204 Grade R to Grade 4 learners were randomly selected from all those registered at Sicelo Primary School in the town of Meyerton. An exposure model developed in a recent study in adults in the same area was used to estimate levels of Mn exposure. Data were collected using questionnaires, and included demographic characteristics, developmental milestones, and residential information. Motor and cognitive skills were assessed using a paediatric balance scale, grooved pegboard, childrens' memory scale and the Wechsler Intelligence Scale for Children. The study participants were divided into three exposure groups (low, moderate and high) and the outcomes were compared amongst them. Categorical variables were analysed using Fisher's exact test. Continuous variables were analysed using the Kruskal-Wallis test. Associations were measured using multivariable linear regression analysis.

Results

Ninety-one children participated in the study (response rate of 44.6%). The demographic characteristics of the three exposure groups were homogenous - all participants were Black Africans and there were no statistical differences between them regarding home language, grade, age and sex. There were statistically significant differences between the groups regarding mothers' occupation (p=0.002), fathers' occupation (p=0.008), duration of pregnancy (p=0.020), birth weight (p=0.045), being breastfed (p=0.003), and achieving developmental milestones (p=0.015). The Mn normalised 4-year mean Mn levels used to categorise the participants into exposure groups were also significantly different between the groups (p=0.001). The mean scores per section for all the cognitive tests were below the standard mean of 100 ± 15. There was a positive relationship between the time taken to complete the grooved pegboard test and Mn exposure group, and a negative relationship between cognitive outcomes and exposure group. The β coefficients from the multivariable linear regression models for motor and cognitive outcomes indicated that there were no statistically significant associations between Mn exposure category and motor and cognitive development.

Conclusion

This study laid a foundation in neurodevelopmental testing of children in an Mn exposed community. The findings are in line with those from previous similar studies, in that no significant associations between exposure and either motor or cognitive outcomes were identified. Further research, using larger sample sizes, and unexposed comparison groups should be conducted.

ACKNOWLEDGEMENTS

A project of this magnitude cannot be completed alone. I acknowledge Prof. Gill Nelson and Prof. Brad Racette whose work in this field initiated an interest in the subject. Their support and assistance during this research are greatly valued. To Wendy Dlamini who supported me during the daunting process of data analysis, thank you.

Without Prof. Brad Racette's financial support, through a NIEHS grant, this work would have not been possible.

I would like to express my gratitude to Katherine Botha and the Pick and Pay Food for the Nation project for sponsoring the food hampers that were given to the parents as a sign of appreciation. The University of Witwatersrand Faculty Research (FRC) grant made it possible for me to purchase the toys for the participating learners.

I am grateful to my family for supporting me during the implementation of the research, to the management and staff of Sicelo Primary School for making their premises available, and especially to the learners and their families without whom this study would not have been possible.

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CHAPTER 1. INTRODUCTION

The aim of this chapter is to describe the occurrence and uses of manganese (Mn) and the effect that its exposure has on human health – focussing on child development. This is done by exploring the literature and describing previous studies that informed the need for this study.

Background

Manganese and its sources

Manganese is a naturally occurring heavy metal and an essential micronutrient for humans and other living organisms.[1,2] It plays a significant role in normal growth and development, especially brain development.[1] The main source of Mn is diet, as it is present in numerous readily available foods, such as leafy green vegetables, legumes, rice, nuts, milk and even chocolate.[2]

Manganese is also found in well (borehole) water, which may be a source of drinking water [3] as well as in Mn mines and ferromanganese smelters. The industries in which workers are at high risk of exposure to Mn and, therefore, adverse health effects, are ferromanganese smelting, iron mining, the steel industry, battery assembling, and welding.[4–6] People who live close to major roads and highways can be exposed to Mn in dust emitted from vehicles that use fuel that contains methylcyclopentadienyl manganese tricarbonyl (MMT). [7,8] Exposure can therefore occur directly through work-related activities, or indirectly from Mn in the environment. Other sources of exposure include pesticides that contain manganese sulphate. [9]

Manganese ore is mined in South Africa where more than 80% of the world's known Mn resources are found, in the Northern Cape province.[10] The large Mn mining industry, and consequent employment opportunities, result in many families living near Mn sources - in mining towns in the Northern Cape province or in settlements close to ferromanganese smelters. There is a high risk of exposure to Mn for both workers in Mn industries and their families in these areas. Children are also exposed

in these areas – either because they live near the Mn sources or because the schools that they attend are located near Mn industries.[11–13]

Ingestion vs inhalation

Manganese levels in the body are tightly regulated by the biliary system.[2] Manganese deficiency is rare because it is available in a wide variety of foods; babies obtain Mn from human milk and/or milk formula which contain Mn as an additive.[2] When ingested, Mn passes through the biliary system[2] - the body's homeostatic control centre[14] and excess Mn is excreted. However, when inhaled, Mn bypasses the biliary system and passes through the blood brain barrier, potentially causing neurotoxic effects[2]. High Mn levels result in accumulation and damage to the basal ganglia[5,15] - structures in the brain that are primarily responsible for motor control as well as motor learning, executive functions, and behaviour and emotions.[14,15]

How is Mn exposure measured?

Human exposure to Mn can be estimated by measuring the amount of Mn present in soil, water, dust, and air particles in the environment. A wide array of tools for measurement are available, from fixed air filters in specific locations to devices that can be placed in homes or carried by individuals.[1,16–18]

Biomarkers for Mn exposure can be measured in blood, saliva, hair, nails, bone, and teeth. Most studies have used Mn levels in blood to estimate exposure.[1,1920] However, blood Mn as a biomarker of exposure reflects only recent exposure.[1,21,22] Manganese levels in hair and nails reflect longer-term, cumulative exposure because 1) they are slow growing, and 2) sulphur-rich keratin (the protein from which they are made) has a high affinity for metal cations.[21]

Factors associated with increased Mn levels

In addition to the amount and mode (ingestion or inhalation) of Mn, sex and age are associated with blood Mn levels.[23] Analysis of the data from the USA National Health and Nutrition Examination Surveys (2012 and 2013), which included 7 720 participants aged 1 to 80 years, found that being female and aged 6 to 12 years were significantly associated with higher blood Mn levels.[23]

Health effects of excess Mn exposure

Excess exposure to Mn, described primarily in occupational settings [4,24–26] can adversely affect cognitive and motor functioning.[2,4,26,27] The term 'manganism' was used by Rodier in 1955 to describe the array of symptoms that closely resembles that of parkinsonism, in miners with high occupational exposure to Mn.[26] Exposure to Mn at levels lower than those described in miners by Couper in 1837 [28] and by Rodier,[26] has been associated with impaired cognitive functions, and gross and fine motor performance.[15,26,29]

In 2008, the time-weighted average (TWA) occupational exposure limit (OEL) for Mn dust in South Africa was set at 5 mg/m^3.[10] The limit has not been adjusted since 2008, and there is no environmental exposure limit.[10]

Exposure to Mn dust and fumes is therefore a public health concern that has not been adequately studied to inform policy makers about the level of Mn exposure below which neurological health effects are unlikely.[17,18]

Literature Review (studies on effects of environmental Mn exposure)

Although studies have been published on the health effects of Mn exposure in adults,[6,17,18,30–32] the majority have been in occupational, rather than environmental settings, [4–6,24,25,30,32–34] and very few have investigated the health effects of environmental Mn exposure in children.

Studies in adults

Studies in adults have shown an association between chronic environmental Mn exposure and impaired motor function.[35] Eighteen of 210 studies that were included in a meta-analysis of the effect of environmental exposure to Mn on motor and cognitive outcomes of adults, published in 2021[36,] reported a negative relationship between Mn exposure and cognitive and motor functions ($p<0.001$). [36] The findings from a recently published community-based study in adults in South Africa[17,18,31] suggest that there are negative effects on neurologic health from Mn exposures that are lower than the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit for Mn of 0.1 mg/m^3.

Manganese exposure in children

Consequences of overexposure to Mn in children include hyperactive behaviour [37,38] and memory difficulties.[1] Cognitive deficits related to Mn exposure include attention deficit,[39] impairment of verbal memory[40] and learning, difficulty with executive functioning, impaired working memory[41] and poor intellectual functioning.[41–44]

Children have a higher risk of Mn accumulation in tissues than adults due to their proportionately higher respiration and air intake levels.[43] Excessive exposure in the pre- and post-natal periods has been shown to lead to deposits of Mn in the striatal and hippocampus brain regions.[1] High Mn concentrations may also alter tissue homeostasis of other essential metals, such as iron (Fe), that are important for normal development.[1]

The mechanism that regulates homeostatic balance by Mn excretion is not fully developed in children.[16] The literature describes children as aged 0-18,[1] where physical growth still takes place, hormonal changes are described to start at 10 years of age, where the child then goes into puberty. They may also be at a higher risk of Mn toxicity after exposure because of the effects on developmental myelination in the frontal cortex and subcortical connections, which are important for cognitive development.[43]

Systematic reviews of child studies

Two systematic reviews of the health effects of Mn exposure in children have focussed on the biomarkers used and neurodevelopmental outcomes.[1,19] In a systematic review, Coetzee et al. (2016) evaluated studies published in English that used a biomarker-based measurement of environmental Mn exposure.[1] They measured at least one neurological outcome in children aged 0-18 years and concluded that hair was the most consistent and valid biomarker. Hair has practical advantages over other tissues because it is easier to collect and store[45]. They also stated that there was a need for more research on neurological outcomes in children due to environmental exposure to Mn. This was echoed by Leonhard et al. (2019), who reviewed epidemiological studies on neurodevelopmental outcomes related to Mn exposure during childhood development.[19] Contrary to Coetzee et al.[1] though, Leonhard et al. reported that higher MnH levels (Mn from hair) were associated with lower intelligence quotient (IQ) scores but concluded that the available evidence was

not convincing enough to establish a negative causal association between childhood Mn exposure and intelligence.[19]

Zoni et al. (2013), in a thematic review, agreed with Coetzee et al.[1] that, overall, research suggests that there is an inverse association between cognitive performance and Mn exposure.[29] They highlighted the difficulty in comparing studies due to the different tests used to measure outcomes and the different sources of Mn exposure. Nevertheless, they confirmed that Mn exposure is related to cognitive, motor, and behavioural deficits in children, and recommended that strategies to reduce Mn exposure be explored.

Effect of Mn exposure on cognitive development in children

Cognitive development, which includes development of the ability to attend to external stimuli and focus, working memory, spatial placement, impulse inhibition, and the development of executive functioning, is negatively affected by exposure to Mn.[14,46]

The most frequently studied neurodevelopmental outcome amongst children, related to Mn exposure, is IQ.[1,19,29] The most frequently used tool to measure IQ is the Weschler Intelligence Scale for Children (WISC). In six of the 23 studies in the three reviews discussed above, there was an inverse correlation between Mn exposure and IQ score using the WISC.[1,38,47–52]

Studies on children exposed to ambient Mn in Brazil,[16,38,52] Mexico,[11,12,42,53] Italy,[54] the US,[13,55,56] Canada[37,51,57] and Bangladesh[3,37,47,58,59] have reported neurobehavioural development effects, such as lower full-scale IQ, and slower perceptual reasoning and processing speed.[1,29]

The need to carefully measure the continuum of exposure and children's health was emphasised by Coetzee et al. (2016)[1] who suggested that there was an inverted U-shaped association between Mn exposure and child health, neurobehavioural development, and cognitive outcomes.[1]

Effect on fine and gross motor development in children

Cognition in children is not the only function that is affected by Mn exposure. Both fine and gross motor function are adversely affected. Specifically, balance and fine motor development, including hand and finger dexterity, and motor integration are affected,[29,54,56] for example, a reduction in hand dexterity was observed in Italian adolescents living near a ferroalloy plant in a study that was published in 2012.[54]

Various studies have demonstrated adverse motor effects associated with Mn exposure in children. The inverse relationship between fine motor performance and Mn exposure has been described in studies conducted in Italy,[54] Mexico,[42] and the USA.[60] Two studies in Ohio, USA analysed Mn and lead (Pb) in blood and hair and reported that Mn in these samples was significantly associated with impaired balance.[55,56] Standridge et al. (2008) measured Mn exposure in hair and nail samples after postural balance testing.[56] In a second study by Rugless et al. (2014), exposure was measured using blood and hair samples, and time weighted distance (TWD) from the ferromanganese plant. All three measures of Mn exposure were significantly associated with poor balance.[55] Conversely, Parvez et al. (2011), in a study on children exposed to Mn in drinking water, did not find a significant association between Mn levels in blood and nail samples, and motor function.[61]

Studies in South Africa on Mn exposure and children

As mentioned, there have been very few studies on Mn in children in South Africa, none of which has investigated health effects. Only three studies have been conducted in South Africa, with a focus on exposure levels.[8,62,63] Batterman et al. (2010) measured Mn and Pb levels in blood of children from grades 3 to 6 living in Durban, South Africa; exposure was from petrol fumes from vehicles.[8] They reported a racial difference in Mn exposure - black African children had lower blood Mn levels than Indian or Coloured children, possibly reflecting differences in traffic and air pollution exposure, and dietary and socio-economic differences.[8,62]

Two studies by Röllin et al., published in 2005 and 2007, respectively, investigated blood Mn levels of children in different locations in South Africa.[62,63] The first study found that blood Mn levels of Grade one children, and concentrations of Mn in soil and dust samples, were higher in Johannesburg than in Cape Town.[62] Importantly, the blood Mn levels of 4.2% of children in Cape Town and 12.5% of children in

Johannesburg were the same or higher than the upper normal reference value of 14µg/L specified by the Agency for Toxic Substances Disease Registry.[62] In the second study, the authors analysed the blood Mn concentrations of selected children in Johannesburg, Cape Town, Kimberley and the rural Northern Cape province.[63] Race, sex, and environment (rural vs urban) confounded the relationship between blood Mn level and environmental exposure levels. The levels of Mn in the blood of children in the four locations varied, and they could not find a consistent relationship between the Mn levels in the blood across the sites.[63] All three studies used Mn in blood as a biomarker for exposure, which is limited in its use for quantifying cumulative exposure to Mn,[21,49] and none investigated neurological or other health effects.[8,62,63]

Factors associated with child neurodevelopment

When studying the neurodevelopment of a child, it is important to consider all factors that influence developmental outcomes. The development of the central nervous system (CNS) is affected by both genetic factors and the physical environment. The environment (care and stimulation) and socioeconomic status (SES) of the family also influence a child's ability to learn.[64]

Child development risk factors have been identified as related to poor maternal nutrition, exposure of the mother to environmental toxins during pregnancy, low birthweight, and childhood undernutrition. Social aspects like cognitive stimulation or child learning opportunities, maternal depression and exposure to violence has been linked to stunted development.[65]

Maternal IQ has been linked to child neurocognitive development, and both home environment and maternal IQ have been shown to affect child cognitive development.[64]

Effect of antiretroviral treatment

In South Africa, HIV/AIDS is another important factor to consider when measuring neurodevelopmental outcomes. HIV-infection in children is associated with cognitive defects, motor deficits and visual, language, and learning disorders.[66] This is supported by the findings from a study in Uganda, where HIV-infected children younger than seven years had deficits in all measures of neurodevelopment.[66]

However, antiretroviral therapy (ART) that is administered for longer than 10 months has been associated with a reduced risk of impairment in fine motor, receptive language, expressive language, and lower general early learning composite scores.[66] It is therefore important to consider both HIV/AIDS status and ART when assessing neurodevelopment of children.

In summary, while several studies on the health effects of Mn exposure have been conducted in adults, very few have been conducted in children, and none have been conducted on children in South Africa. Studies have shown an association between Mn exposure and adverse neurological outcomes in adults[32,34] but children who are exposed to Mn in the environment may be at a higher risk of adverse neurological outcomes such as emotional, motor coordination and cognitive problems, because of their higher respiration rate and the fact that myelination of the neurons in the frontal cortex has not fully finished.

Justification for the study

The prevalence and severity of motor dysfunction, cognitive control, mood, and behavioural dysfunction were recently investigated in adults in a community located near a ferromanganese smelter in Gauteng province, South Africa.[18,31] The study provided evidence for an association between environmental Mn exposure and parkinsonian motor dysfunction. The authors concluded that exposure to environmental Mn at levels lower than the current occupational exposure thresholds in the US of 50µg/m^3 may be associated with clinical parkinsonism.[18] The results from the cognitive testing provided evidence that environmental Mn exposure was associated with cognitive dysfunction.[17]

Due to where they live and where they go to school, the children in this area are continuously exposed to Mn, which might place them at an even higher risk of adverse health effects than the adults.[1] The paucity of research on the effects of Mn in children, and in South Africa specifically, highlighted the need for a study on children. The adult study in Meyerton[17,18,31] had already raised community awareness of the health effects of Mn exposure. In addition, exposure data were collected over a period of several years in this study. This created an opportunity to conduct the study discussed in this report.

Aim

The aim of this study was to assess the effects of exposure to ambient Mn on the cognitive- and motor-development of children living and being schooled near a ferro-manganese smelter in South Africa.

Study objectives

The objectives of the study were to 1) use the exposure model developed in the adult study to estimate the levels of Mn to which children aged 5 to 10 are exposed; 2) assess motor development by measuring fine motor speed, visual motor integration and balance of the children; 3) assess cognitive development by measuring the children's cognitive performance; and 4) investigate the association between Mn exposure levels and neurodevelopmental outcomes.

CHAPTER 2. METHODS

The aim of this chapter is to describe the data collection procedures, the tests used to measure cognitive and motor functions, and the statistical methods used to analyse the data.

Study setting

This was a cross-sectional study, conducted at Sicelo Primary School in the Midvaal Municipality of Gauteng Province. The school is in the town of Meyerton, which is located 56 km south of Johannesburg, and is attended by learners that reside in the nearby townships of New and Old Sicelo residential area and informal settlement, De Deur, and Rustervaal. A large ferro-manganese smelter is situated 2 km from the school (see Figure 2.1). It is located immediately west of the R59, a provincial road connecting Vereeniging to Alberton, and falls within the jurisdiction of the Midvaal Local Municipality - part of the greater Sedibeng District Municipality.

The smelter has been owned by several companies since it was built in 1951 and is built on 57 hectares of land.[67] In 2021, the owners of the smelter, South32, announced that the smelter's production had decreased by 16 000 tons, from 69 000 to 53 000 tons, in 2020. Until the smelter closed in 2020, because of the COVID-19 pandemic, the 81 MVA furnace could produce 120 000 tons of High Carbon Ferromanganese (HCFeMn) per year.[68] When fully operational, the smelter provided employment to approximately 300 people.



Figure 2.1 Map of Meyerton, indicating Sicelo Primary School and neighbouring settlements

Study population

The study population comprised all children aged 5-10 (Grades R to 4) enrolled at Sicelo Primary School in 2021, who had not been diagnosed with neurological disorders or were more than two years older than the age expected for the grade in which they were in. Learners in Grade 3 and 4 who were older than 10 years are also indicated in the number excluded (Table 2.1). The community of interest in this study is exposed to $PM_{2.5}$-Mn at different levels and a difference in normalised 4-year mean Mn exposure levels.

Table 2.1 Study population, indicating the numbers of learners included, excluded, and sampled, by Grade

Grade	Total no. of learners	No. excluded	Study population	Sample size (20%)
R	75	0	75	15
1	264	1	263	55
2	252	0	252	50
3	283	21	262	53
4	286	139	147	31
All	1 160	161	999	204

Study sample

Sample size calculation

The sample size necessary for this study was calculated using a prevalence of 22% obtained from a study conducted in Montevideo in (2010).[69]

A formula to calculate the sample size, using prevalence in cross sectional studies, was used,[70] i.e.

n=$\frac{Z^2P(1-P)}{d^2}$, where Z is the statistic corresponding to level of confidence, P is expected prevalence (0.22) and d is precision (corresponding to effect size). The level of confidence aimed for was 95%, which equates to a level of precision of 5% (0.05). The Z statistic corresponding a 95%CI is 1.96.

n= $\frac{1.96^2\ [0.22(1-0.22)]}{0.05^2}$ = $\frac{3.8416[0.22\times0.78]}{0.0025}$ = $\frac{3.8416\times0.1716}{0.0025}$ = $\frac{0.65921856}{0.0025}$= 264

Considering the limited time available due to the COVID-19 pandemic restrictions on schooling in South Africa, and the fact that only Grades R- 4 from the total group of Grade R-7 were eligible due to the age parameters, the percentage that represented 264 of the total student body was estimated to be 20%. Thus, a sample of 20% of each grade was selected, i.e., 204 learners in total.

Sampling method

A computerised random number generator was used to select a 20% proportional sample of learners from each grade. A list of learners in each grade was obtained from the school principal. Information comprised surname, first name, sex, date of birth, and mobile phone number, where available.

Data collection tools

The measurement tools used are summarised in Table 2.2, which indicates what data were collected using each tool, and the time that it took to complete each test. The selected tools were not standardised for a South African community, therefore tests that did not have a language contingent were selected. The tools have been used in similar research. Figure 2.2 illustrates the measurement tools (Appendix B) visually.

Table 2.2 Measurement tools

Data category	Tool	Data collected	Duration (minutes)
Socio-demographic characteristics	**Interviewer-administered questionnaire**	Socio demographic information: age, sex, race, home language and grade. Birth history, developmental history, education history, current medication. Residential history used to match to closest available geocoded and Mn estimated address.	30
Motor function	**Grooved pegboard**	Fine motor dexterity	10
	Paediatric balance scale	Static standing balance	10
Cognitive function	**Children's memory scale** Dot Locations learning Dot Locations total and Dot Locations delayed. Faces immediate Faces delayed Numbers Sequences	Executive function and cognitive control Visual immediate memory Visual delayed memory Working memory, attention, concentration	30
	Weschler intelligence scale for children (WISC V) subtest: Matrix reasoning	General IQ	5



Figure 2.2 Measurement tools used to assess cognitive and motors skills of children

Questionnaire

The questionnaire was designed to provide information regarding social demographic characteristics (age, sex, etc.), birth history, developmental history, educational history, and residential history (Appendix C). The guardian was guided through the questionnaire by the investigator who asked the questions and completed the questionnaire. The content of the questionnaire was based on the literature review and knowledge of human development. The questionnaire was paper-based tool to ensure optimal use in rural environment.



Figure 2.3 Administration of questionnaire

Grooved pegboard

The Lafayette grooved pegboard (GP) was used to assess fine motor skills and dexterity (Appendix B). This is a standard device. The unit consists of 25 holes with randomly positioned slots and 25 key-like metal pegs. Self-reported handedness (left or right) was recorded to indicate the dominant and non-dominant hand. Each child was instructed to start with his/her dominant hand, pick up the peg and place it in the hole. Only one hand could be used; the other hand could be used to hold the pegboard. The investigator timed the task up to 5 minutes. If it took longer, the test was discontinued. Thereafter, the non-dominant hand was tested in the same manner.



Figure 2.4 A learner completing the grooved pegboard test

The GP score is the sum of time taken to complete the task in seconds (t), the number of pegs placed (n), and the number of mistakes made (m).

Paediatric balance scale

The paediatric balance scale (PBS) (Appendix B) is a modification of Berg's Balance Scale[71] developed as a balance measure for school–age children.[72] The scale consists of 14 tasks. The score for each task is summed to get the total score. Equipment needed to execute this test is inexpensive,[73] and comprises a printed scale sheet, a chair, a bench, two cardboard footprints, masking tape, measuring tape, a stepping block, and an object to pick up from the floor.

The PBS consists of 14 tasks that are scored by the investigator according to set criteria. Multiple trials are allowed after the item is demonstrated by the investigator. The minimum score is 0 (not achieved) and the maximum score is 4. The description of the 14 tasks and the scoring criteria can be found in Appendix B.



Figure 2.5 Paediatric balance scale tasks: placing alternate foot on stool, standing one foot in front, standing on one foot

A child's performance should be scored based upon the lowest criteria, that describe the child's best performance. The 14 scores are summed to give a total balance score. The maximum score that can be achieved is 56. Lower scores indicate difficulty in maintaining balance. It is postulated that, by the age of 7 years, balance skills are fully developed and a score of 56 is expected.[71,72]

Children's Memory Scale

The Children's Memory Scale (CMS) (Appendix B) is a comprehensive learning and memory assessment designed to evaluate learning and memory functioning.[74] It is divided into visual memory, verbal memory and attention and concentration. Tests measure both immediate and delayed memory. The scale provides an indication of how long it takes to learn a new concept. The equipment consists of two books with test plates, a page with a 3 x 4 grid for ages 5 to 8 years, and a 4 x 4 grid for ages above 9 years, eight blue discs, and a test administration and scoring manual.

The tests chosen for this study from the CMS were:

a) Dot locations, immediate recall, that uses the 3x4 or 4x4 grid, blue discs, and test plates. The participant is shown a stimulus card showing the grid with dots in certain locations. The card is taken away and the participant places the discs where they can remember the dots were. The participant is told to remember this for later reference.

b) Faces immediate recall, uses visual prompts. The participant is showed a set of faces, one by one, after which they are shown a series of faces where they must respond with a yes if the face was one of the original set or no if they were not.
c) Numbers, which corresponds closely to the digit span test in the WISC. The participant is asked to recall and repeat a series of numbers, firstly forward and then as set backwards.
d) Sequences is completed by the investigator requesting the participant to perform different verbal sequential tasks like counting from 1 to 10 as quickly as they can, naming the letters of the alphabet, naming the days of the week forward and backwards, etc.
e) Dot locations delayed recall has the participant recall the pattern of discs placed at the beginning of the test sequence without seeing the stimulus card again.
f) Faces delayed recall has the participant look at pictures of faces and having to respond with a yes if the face was one of the original sets that the participant viewed or no if it was not.



Figure 2.6 Dot locations: a child placing discs on a grid after viewing a stimulus card

The CMS is a standardised assessment that provides information on visual and verbal memory. Only the visual tests were administered because they do not have a language aspect. Each test was scored, and a raw total score was obtained. The score was then translated to a scaled score.[74] A scaled score represents the number

of correct answers (raw score) converted using a standardised, consistent, and norm-based scale found in the manual of the test. These scaled scores are presented as integers from 1 to 15. To obtain the standard score, as presented in Figure 2.8, the scaled scores of 2 tests were summed, using the conversion table in the CMS manual.[74] These standard scores are presented as integers from 50 to 150.

The Wechsler Intelligence Scale for Children (WISC)

The WISC (Appendix B) is an individually administered intelligence (IQ) test for children aged 6 to 16 years. It is less dependent on language or education than other IQ estimators.[75]

The matrix reasoning subtest of the WISC was used. This test consists of a set of test plates and a scoring manual. Matrix reasoning is a type of visual-spatial problem-solving exercise. It involves a series of figures in which there is a pattern, with one figure in the series left blank. The problem is solved by determining, from an array of possibilities, which figure would complete the series or pattern.[76] The test measures visual processing and abstract, spatial perception, and may be influenced by concentration, attention, and persistence.



Figure 2.7 Matrix reasoning stimulus card: a child pointing to the missing object

The matrix reasoning test from the WISC III test battery was used. The number of correctly identified options are summed to give a raw score and translated to a scaled score.[76] The scaled scores are presented as integers from 1 to 15. The WISC is only standardised for children aged 6 to 18 years.

Data collection

Data were collected during one session with the participant and guardian present. In Figure 2.8, the process of assessment of the participant, and the scoring of children's memory scale are illustrated in a flow diagram.

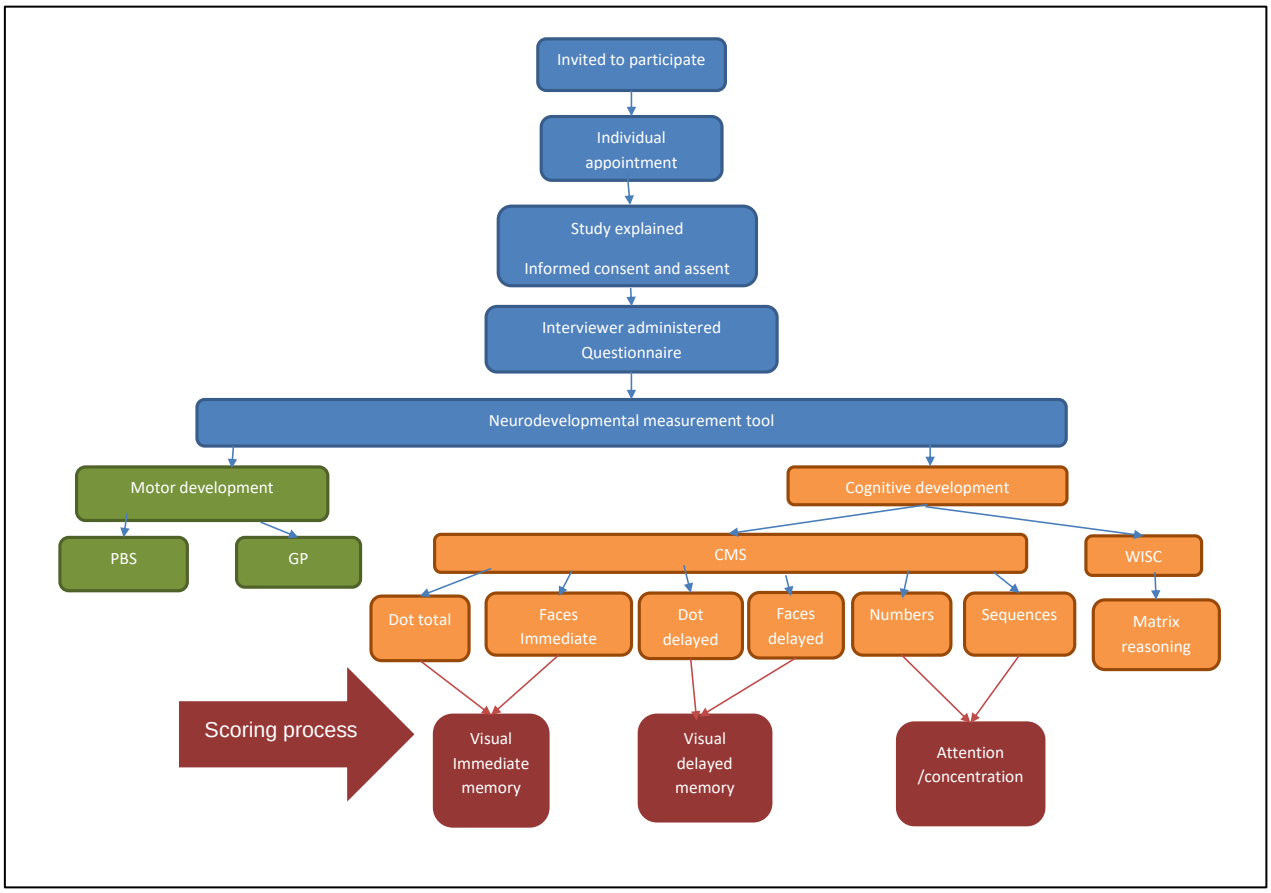

Figure 2.2 Flow diagram showing the process of assessment and scoring of Children's memory scale

PBS: Paediatric balance scale; GP: Grooved pegboard; CMS: children's memory scale; WISC: Wechsler Intelligence scale for children

Process of recruitment and assessment

The investigator recruited participants by telephoning the parents or guardians of the selected learners to request appointments to explain the study and ask for their consent to participate. Learners whose parents/guardians did not have telephone

numbers were given an information letter (Appendix D) to take home. The letter had a detachable return slip with space for a contact number. Appointment letters with the date and time of appointment were also sent home with the child, to contact the parent.

Appointments were scheduled, for those who agreed to participate, at times after school hours, on weekends, and during school holidays. The informed consent (Appendix E) and assent (Appendix F) were obtained after explaining the aim and procedure of the study to both the parent and child. The parents received a copy of the information sheet and informed consent.

The venue was prepared by setting up three stations. The first station was for explaining the study, obtaining consent and assent, and completing the interviewer-administered questionnaire. The second was a station with two desks placed at a 90-degree angle and two seats: one for the investigator and one for the participant. The third station consisted of a chair, a bench, and a step. The cardboard feet of the PBS were placed on the floor and a line of masking tape was stuck to the floor for administering the paediatric balance scale.

The questionnaire was administered by a trained occupational health nurse. The assessment procedure was explained to the participant. The investigator started with the dot location immediate recall and faces immediate recall subtests of the CMS, after which the GP test, the PBS, and the matrix reasoning test were completed. The numbers and sequences subtest were completed before returning to the dot location delayed recall and faces delayed recall. This allowed for a time lapse of 30 minutes between the immediate recall and delayed recall tests.

When all tests had been completed, as a sign of appreciation, the parent/guardian was given a food hamper, and the learner was given a drawstring bag with a jump rope and a set of Duplo blocks.

Measurement

Care was taken to comply with all COVID-19 precautions and to prepare the environment to perform the tests under the best possible conditions for optimal attention and concentration. Good illumination was provided, and external noise was limited.

Estimation of exposure to Mn

Cumulative PM2.5-Mn exposure was estimated for each study participant, using the Mn exposures for each residential group that were calculated and described by Racette et.al. (2021).[18,31] The model for estimating $PM_{2.5}$-Mn levels was developed, using historical air quality monitoring data, recent continuous Mn air monitoring in the Meyerton area from October 2015 to May 2018, historical meteorological data, and data on the height and emissions of Mn from each of the two stacks of the ferromanganese smelter.[18] This model was used to predict Mn-containing particulate matter <2.5 µm aerodynamic diameter (PM2.5-Mn).

The investigator matched the participants' residential addresses as reported in the questionnaire to those closest to the participants in Racette et al.'s study[18,31] to obtain approximate Mn exposure values reported as 4-year mean normalised Mn exposure value, which were used to group the participants into three exposure groups: high (0.07 to 0.32 ng/m^3), moderate (0.04 to 0.05 ng/m^3) and low - an area that was allocated a reference value in the study by Racette et al.(2021),[17,18,31] because it is further than 10 km from the smelter.

The first group (high exposure) lived in the residential settlement next to the school. In this group, street addresses were matched to addresses where exposure measurements were available.[17] The second group (moderate exposure group) was the informal settlement next to the R59, where there are no formal street names and numbers. Residential environmental Mn exposure data from the study by Racette et.al. (2022) were used.[17,18,31] The low group (reference) comprised De Deur and residences that were located further than 10 km from the smelter. This group therefore had no 4-year mean normalised Mn exposure value.

Data management

Data from the questionnaire and the other measurement tools were coded and labelled (where appropriate) and entered onto an MS Excel spreadsheet.
The data were Imported into STATA 15.1 from MS Excel for analysis.[77] Prior to analysis, the data were cleaned. Data entry errors were identified by tabulating, and looking for invalid values, etc. Table 2.3 outlines the data management and analysis. The names of statistical tests used for analysis are included. The tests are discussed under the statistical analysis section.

Table 2.3 Data management and analysis

Objective	Outcome variable (exposure)	Variable type	Outcome variable	Variable type	Statistical test
1. To use the exposure model developed in the adult study [17,18,31] to estimate the levels of Mn to which children aged 5 to 10 years are exposed.	Residential address matched to closest available address with a linked Mn normalised 4-year mean. Section variable that represents the Mn exposure group that is linked to the residential address, labelled as high, moderate, and low. The section variable is described according to the outcome variables.	Continuous Categorical	Sex Race Level of education Age group Home language Mother's highest level of education. Father's occupation Exposure to smoke during pregnancy Alcohol use during pregnancy Birth complications	All categorical	Descriptive analysis. Student's t test and Kruskal Wallis test for continuous variables. Fischer exact test for categorical variables.
2. To assess motor development by measuring fine motor speed, visual motor integration and balance of the children.	Mn exposure group	Categorical	Fine motor speed (GP for dominant and non-dominant hand. Balance (PBS total score)	Continuous Continuous	Descriptive analysis. Kruskal Wallis test.
3. To assess cognitive development by measuring the children's cognitive performance.	Mn exposure group	Categorical	Cognitive control (visual immediate recall, and attention and concentration) Working memory (Visual delayed recall and Attention and concentration) Executive function (attention and	Continuous Continuous Continuous	Descriptive analysis. Kruskal Wallis test.

			concentration, and matrix reasoning)		
To investigate the association between Mn exposure levels and neurodevelopmental outcomes.	Mn Exposure group Models adjusted for: Age Sex Exposure to smoke during pregnancy (Yes or No) Mother's use of alcohol during pregnancy (Yes or No) Gestation (full term or preterm) Mothers level of education Fathers' occupation	All categorical	Motor function: - Balance (total balance score) - Fine motor and visual motor integration (GP score in seconds) Cognitive function	Continuous Continuous Continuous	Multivariable linear regression

Mn= Manganese; GP= Grooved pegboard; PBS= Paediatric Balance scale; CMS= Children's memory scale

Statistical analysis

Descriptive statistics

Variables used to describe the demographic characteristics of the participants were age, sex, race, home language, and grade. Variables used to describe the developmental history of the participant were mother's highest level of education, father's occupation, mother's occupation, mother's report of smoking and use of alcohol during pregnancy. The duration of the pregnancy and manner of birth, complications at birth and reaching of developmental milestones were also described as categorical variables.

The categorical variables were described using frequencies (n) and percentages (%). For the categorical variables, the Fisher's exact test was used to describe differences in proportions.

Variables obtained from neurobehavioural testing were the scores from the PBS and GP tests for balance and fine motor skills, respectively. The variables used to describe cognitive performance were the scores for visual immediate memory and visual delayed memory for working memory and cognitive control. These, along with attention and concentration scores, were obtained from the CMS. The matrix reasoning score was used as an indication of general intelligence. All scores were expressed as continuous variables.

The normally distributed continuous variables were described using means and standard deviations (SD) and compared using the Student's t test. Medians and interquartile ranges were used to describe variables with data that were not normally distributed; the non-parametric Kruskal Wallis test was used for comparisons.

Box and whisker plots were plotted to illustrate the scores for the visual delayed memory subtests (dot delayed and faces delayed), the matrix reasoning test, and the GP test. The Mn exposure per area was also depicted using a box and whisker plot.

Inferential statistics

Multivariable linear regression was used to measure the associations between Mn exposure and motor and cognitive outcomes. Mn exposure (independent variable) was categorised into three groups, as described; the dependent variables were the motor test scores, which were continuous variables.

The multivariable linear regression model was built stepwise forward. We first adjusted *a priori* for age and sex in all models as informed by a review of the literature, then examined the effects of adjustment for exposure to cigarette smoke, alcohol during pregnancy, gestation, developmental milestones, mother's highest level of education, and father's employment. Variables were included at 0.05 level in the final model.

We report the multivariable linear regression beta (β) coefficients, with 95% confidence intervals (CI). A two-sided p-value of < 0.05 defined statistical significance for all associations.

CHAPTER 3. RESULTS

This chapter presents the results of the analysis of the data collected on demographic, developmental, residential, cognitive, and motor development of the children who participated in the study. The results are presented in tables and graphs structured to address the objectives of the study, i.e., to describe the environment and nature of the study participants and their Mn exposure, and their motor and cognitive development, and to determine the strengths of the associations between the different Mn exposure groups and neurodevelopmental outcomes.

The participants were divided into Mn exposure groups with 11 participants in the low exposure group, 33 participants in the moderate exposure group, and 47 participants in the high exposure group (Table 3.1). All 91 (response rate of 44.6%) children were Black African. There were no significant differences between the three groups regarding sex, age group, grade, and home language, i.e. the groups were homogenous with respect to these characteristics.

Zulu was the most common home language (n = 36, 39.6%), followed by Sesotho. The participants were Grade R to 4. In the low exposure group, 45.5% (n=5) of the learners were in Grade R. However, in the moderate and high exposure groups learners were more evenly distributed across the grades.

The mean $PM_{2.5}$-Mn concentrations from the long-term particulate air sampling were significantly different *(p=0.001)* between the high and moderate Mn exposure groups.

Table 3.1 Demographic characteristics of the study participants by Mn exposure group (N=91)

Characteristic	All participants		Mn exposure group						
			Low (N=11)		Moderate (N=33)		High (N=47)		P-value[a]
	N	%	n	%	n	%	n	%	
Sex									
Male	45	49.5	6	54.6	14	42.4	25	53.2	*0.612*
Female	46	50.5	5	45.5	19	57.6	22	46.8	
Age									
9 to 10	24	26.4	2	18.2	11	33.3	11	23.4	
8 to 9	21	23.1	3	27.3	6	18.2	12	25.5	
7 to 8	16	17.6	0	-	7	21.2	9	19.2	*0.202*
6 to 7	21	23.1	4	36.4	4	12.1	13	27.7	
5 to 6	9	9.9	2	18.2	5	15.2	2	4.3	
Education									
Grade R	17	18.7	5	45.5	5	15.2	7	14.9	
Grade 1	24	26.4	1	9.1	9	27.3	14	29.8	
Grade 2	30	33.0	3	27.3	9	27.3	18	38.3	*0.394*
Grade 3	7	8.0	1	9.1	3	9.1	3	6.4	
Grade 4	13	14.2	1	9.1	7	21.2	5	10.6	
Language									
Zulu	36	39.6	7	63.6	15	45.5	14	29.8	
Sesotho	33	36.2	3	27.3	13	39.4	17	36.2	*0.143*
Other	22	24.2	1	9.1	5	15.2	16	29.8	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Mn normalised 4-year mean ng/m^3	0.124	0.09	--[b]		0.045	0.001	0.18	0.07	
Minimum	0.04		--[b]		0.04		0.07		
Median	0.10		--[b]		0.05		0.17		*0.001*
Maximum	0.32		--[b]		0.05		0.32		

Mn=manganese; SD=Standard deviation

[a] P-value: Fisher's exact test, or Kruskal Wallis test

[b] No value - area further than 10 km from the smelter

The variables that describe the developmental history of the participants are presented in Table 3.2.

Most of the mothers of participants (n=55, 60.4%) in all three exposure groups had education levels of Grade 11 or 12. In the low exposure group, 45.5% (n=5) of mothers were employed, compared to the moderate and high exposure groups where 72.7% (n=24) and 53.3% (n=25) of mothers were unemployed, respectively. The highest rate of unemployment of fathers was in the high exposure group (n=14, 29.8%).

Alcohol use was higher during pregnancy in the high exposure group (n=14, 29.8%) than in the other two groups. The self-reported alcohol use during pregnancy for all participants indicates that 74.7% (n=68) of mothers reported not to have used alcohol during pregnancy.

Tobacco uses during pregnancy were evenly distributed across the three Mn exposure groups, 9.1% (n=1) in the low exposure group, 9.1% (n=3) in the moderate exposure group and 8.5% (n=4) in the high exposure group.

In all three of the exposure groups, most children were born full term (n=78, 85.7%); 52.7% (n=48) were reported to have had normal birth weights (2.5 - 4.5 kg). Details about birth weights were not known for 36.3% (n=33) of the participants. Most participants (n=75, 82.4%) had not been hospitalised as babies.

Only three children used medication; all for tuberculosis and all were in the high exposure group. Delayed milestone development was reported by guardians for a much higher proportion of children in the low exposure group (n=4, 36.4%) than for those in the high and moderate exposure groups (n=3,9.1%, and n=3, 6.4%, respectively).

However, significant differences between the exposure groups were found for mother's occupation (*p=0.002),* father's occupation (p *=0.008),* gestation period (*p =0.020)*, breastfeeding *(p =0.003),* and developmental milestones (*p=0.015)*.

The highest unemployment rate for mothers was in the moderate exposure group, in which 72.7% (n=24) of mothers reported being unemployed in contrast with the low exposure group (n=3, 27.3%).

The highest prevalence of premature births was in the low exposure group (n=4, 36.4%) along with the highest rate of below average birth weight (n=4,36.4%). The highest prevalence of delayed developmental milestones (n=4,36.4%) was reported in the low exposure group.

Table 3.2 Developmental history of the study participant by Mn exposure group (N=91)

	All participants		Mn exposure group						
			Low (n=11)		Moderate (n=33)		High (n=47)		*P-value*[a]
Characteristic	**N**	**%**	**n**	**%**	**N**	**%**	**n**	**%**	
Mother's education									
None	11	12.1	1	9.1	4	12.1	6	12.8	
Grade 1-10	25	27.5	2	18.2	8	24.3	15	31.9	*0.837*
Grade 11-12	55	60.4	8	72.7	21	63.6	26	55.3	
Mother's occupation									
Unemployed	52	57.1	3	27.3	24	72.7	25	53.2	
Employed	28	30.8	5	45.5	8	24.2	15	31.9	*0.002*
Not known	11	12.1	3	27.3	1	3.0	7	14.9	
Father's occupation									
Unemployed	16	17.6	0	-	2	6.1	14	29.8	
Employed	45	49.5	8	72.7	21	63.6	16	34.0	*0.008*
Not known	30	33.0	3	27.3	10	30.3	17	36.2	
Smoking during pregnancy									
Yes	8	8.8	1	9.1	3	9.1	4	8.5	*0.995*
No	83	91.2	10	90.9	30	90.9	43	91.5	
Smoke exposure during pregnancy									
Yes	14	15.4	2	18.2	8	24.2	4	8.5	*0.138*
No	77	84.6	9	81.8	25	75.8	43	91.5	
Alcohol during pregnancy									
Yes	23	25.3	2	18.2	7	21.2	14	29.8	*0.698*
No	68	74.7	9	81.8	26	78.8	33	70.2	
Gestation[b]									
Full term	78	85.7	7	63.6	27	81.8	44	93.6	*0.020*
Premature	13	14.3	4	36.4	6	18.2	3	6.4	
Birth weight									
Below	10	11.0	4	36.4	3	9.1	3	6.4	
Normal	48	52.7	2	18.2	18	54.6	28	59.6	*0.045*
Not known	33	36.3	5	45.5	12	36.4	16	34.0	

Hospitalisation at birth									
Yes	38	41.8	4	36.4	10	30.30	24	51.1	*0.159*
No	53	58.2	7	63.6	2	69.7	23	48.9	
Breastfed[c]									
No	25	27.5	1	9.1	7	21.2	17	36.2	
Yes	63	69.2	7	63.6	26	78.8	30	63.8	*0.003*
Not known	3	3.3	3	27.3	0	-	0	-	
Hospitalisation as baby[d]									
No	75	82.4	10	90.9	25	75.8	40	85.1	*0.493*
Yes	16	17.6	1	9.1	8	24.2	7	14.9	
Developmental milestones									
Delayed	10	11.0	4	36.4	3	9.1	3	6.4	
Appropriate	52	57.1	2	18.2	18	54.6	32	68.1	*0.015*
Not known	29	31,9	5	45.5	12	36.4	12	25.5	
Medication									
Yes	3	3.3	0	-	0	-	3	6.4	*0.362*
No	88	96.7	11	100	33	100	44	93.6	

Mn=manganese; SD=standard deviation

[a] P-value: Fisher exact test

[b] Types of birth were vaginal and caesarean

[c] Feeding complications included, babies having reflux and “cramps” as a baby

[d] Reasons for hospitalisation included having difficulty breathing, meningitis, and broken arms

Table 3.3 shows the results of the PBS and GP tests (the fine motor tests) of the study participants, as scores. There were no statistically significant differences in the mean scores of the PBS tests between the three Mn exposure groups 51.72, 53.94 and 54.15 for low, moderate, and high exposure groups, respectively. One child in the moderate exposure group was found to have a low PBS score of 38, which indicates impairment of balance.

None of the participants took longer than the 300 second limit to complete the GP test with the dominant hand. However, the maximum time to complete the test with the non-dominant hand was exceeded, with the highest mean score being recorded for participants in the moderate exposure group (53.94). The quickest time for completion of the GP test with the dominant hand was 39.36, by a participant in the

moderate exposure group. As for the PBS scores, there were no significant differences between the mean GP scores for the different exposure groups.

Table 3.4 shows the results of the cognitive assessments, as scores for visual immediate memory, visual delayed memory, attention/concentration, and matrix reasoning.

The CMS manual[74] describes the standardisation of the test (incorporating visual immediate memory, visual delayed memory, attention/concentration). The standardised mean is set at 100 ± 15. The mean scores for all participants for attention/concentration, visual immediate memory and visual delayed memory were 66.24, 82.02 and 82.11, respectively.

The WISC manual[76] describes the standardisation of the matrix reasoning subtest. The standardised mean is 10 ± 3. The overall mean for all participants in this study was 5.40, indicating that general cognitive function of the children was below average.

There were no significant differences between the mean scores for the different exposure groups.

Table 3.3 Motor outcome scores, overall and by Mn exposure group (N = 91)

Test	All participants	Mn exposure group			*P-value*[c]
		Low (n=11)	Moderate (n=33)	High (n=47)	
PBS score[a]					
Mean (SD)	53.78 (2.95)	51.72 (4.61)	53.94 (3.39)	54.15 (1.81)	
Minimum	38	43	38	50	*0.294*
Median	55	53	55	54	
Maximum	56	56	56	56	
Grooved pegboard score[b]					
Dominant hand					
Mean (SD)	98.71 (45.37)	92.72 (34.72)	113.42 (58.27)	89.77 (34.04)	
Minimum	39.36	50.43	39.36	40.3	*0.259*
Median	90.19	90.22	100.66	88.45	
Maximum	290	143	290	176.67	
Non-dominant hand					
Mean (SD)	118.77 (62.05)	127.29 (71.77)	127.28 (58)	110.79 (62.17)	
Minimum	43	54.87	58.86	43.9	*0.272*
Median	103	95.3	117.6	94.62	
Maximum	300	230.83	300	281.47	

Mn=manganese; PBS=Paediatric Balance Scale; SD=standard deviation

[a] Poorer motor performance is indicated by a smaller PBS score. The maximum score is 56

[b] Measured time (seconds) Poorer motor performance is indicated by greater grooved pegboard times.

[c] P-value: Kruskal Wallis test

Table 3.4 Cognitive outcomes, overall and by Mn exposure group (N = 91)

Outcome	All participants	Mn exposure group			
		Low (N=11)	Moderate (N=33)	High (N=47)	*P-value*[e]
Attention & concentration[a]					
Mean (SD)	66.24 (14.02)	71.55 (14.38)	66.09 (13.64)	65.11 (14.21)	
Minimum	50	55	50	50	
Median	63	78	63	60	*0.449*
Maximum	106	88	94	106	
Visual immediate memory[b]					
Mean (SD)	82.02 (13.25)	78.82 (9.77)	83.42 (10.82)	81.79 (15.41)	
Minimum	54	69	69	54	
Median	82	82	82	82	*0.548*
Maximum	112	100	112	112	
Visual delayed memory[c]					
Mean (SD)	82.11 (14.55)	80.82 (8.78)	80.55 (12.42)	83.51 (16.90)	
Minimum	57	69	60	57	
Median	82	82	78	88	*0.713*
Maximum	122	100	109	122	
Matrix reasoning[d]					
Mean (SD)	5.40 (2.44)	5.67 (2.39)	4.98 (2.59)	5.64 (2.36)	
Minimum	2	2	3	2	
Median	5	6	4	5	*0.297*
Maximum	11	9	11	10	

Mn=manganese; SD=standard deviation

[a] Attention and concentration composite score is the sum of numbers and sequences subtest scaled scores. It is an age-scaled score with integers between 50 and 150.

[b] Visual Immediate composite score consists of the sum of scaled scores from Dots total and faces Immediate subtest scaled scores.

[c] Visual delay composite score consists of the sum of scaled scores from Dots delayed and faces delayed subtest scaled scores

[d] Matrix reasoning test is standardised for children 6 and over. Missing 10 values are those of the 5-year-old group.

[e] p-value: Kruskal Wallis test

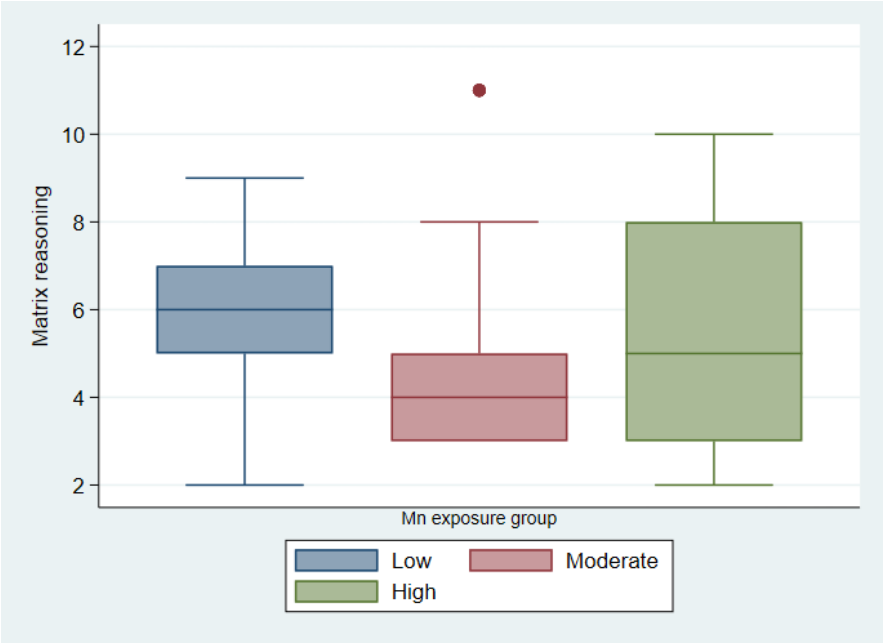

Fig. 3.1 Box and whisker plot of matrix reasoning test, by Mn exposure group,showing median and interquartile ranges, and outliers.

Figures 3.2 and 3.3 illustrate the scores from the subtests of visual delayed memory, dot locations delayed, and faces delayed, respectively. Most of the data points lie below the age-appropriate norm of 10.[74]

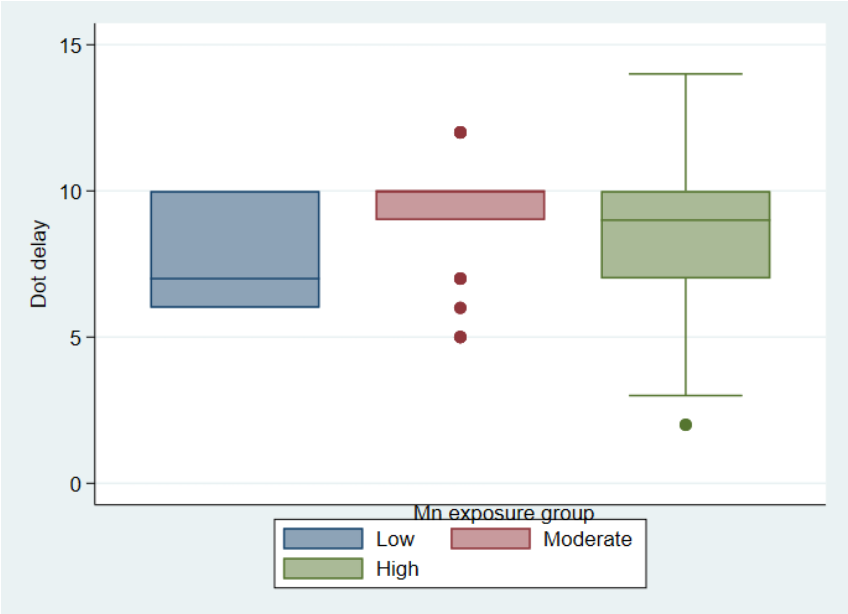

Fig. 3.2 Box and whisker plot of dot delayed test, by Mn exposure group, showing median and interquartile ranges, and outliers

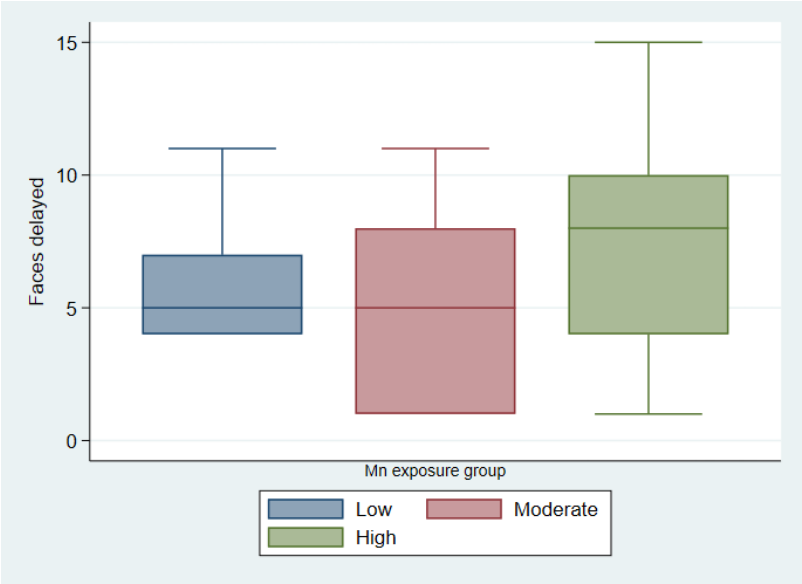

Fig. 3.3 Box and whisker plot of faces delayed test, by Mn exposure group, showing median and interquartile ranges, and outliers

The mean score (time in seconds) for the GP test, using the non-dominant hand, was 118.77. This was 20.06 seconds slower than the mean score using the dominant hand (98.71).

Figures 3.4 and 3.5 illustrate the scores from the GP test for the dominant and non-dominant hands. The median time taken to complete the test did not differ significantly between the three exposure groups: 90.22, 100.66 and 88.45 for the low, moderate, and high Mn exposure groups, respectively.

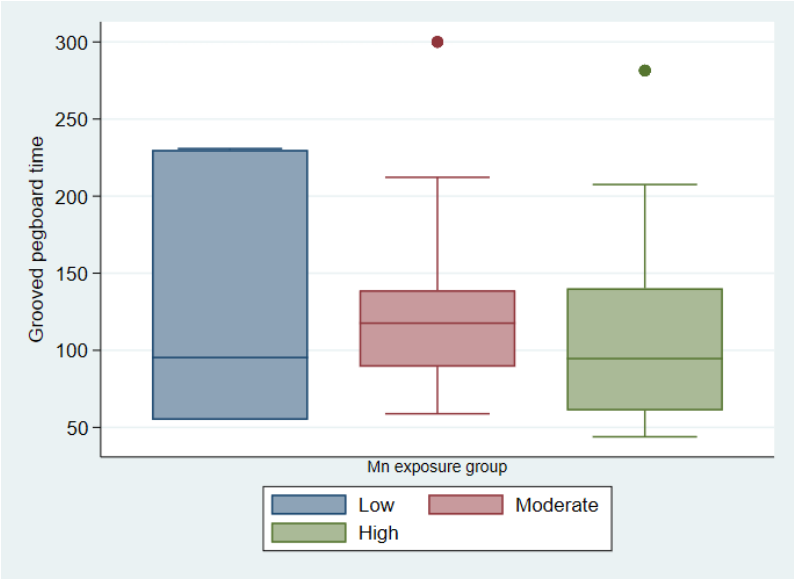

Fig.3.4 Box and whisker plot of grooved pegboard scores for the dominant hand, by Mn exposure group, showing median and interquartile ranges, and outliers

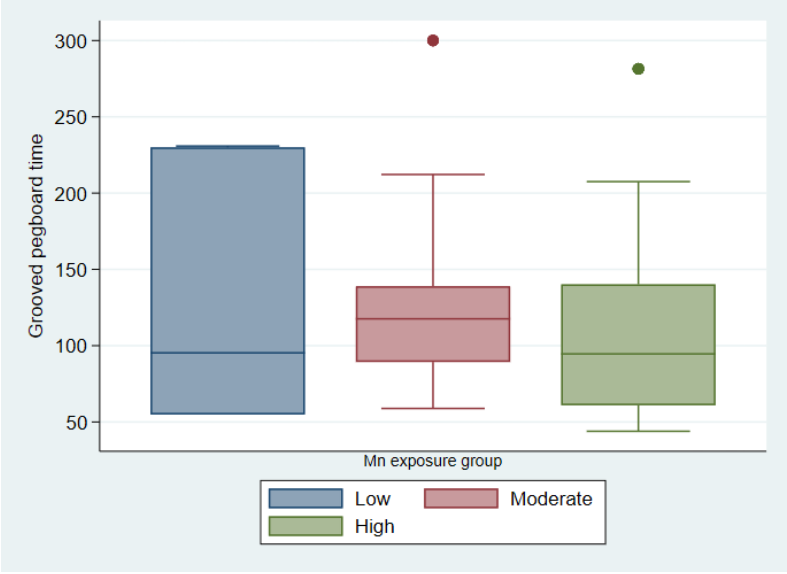

Fig.3. 5 Box and whisker plot of grooved pegboard scores for non-dominant hand by Mn exposure group, showing median and interquartile ranges, and outliers



Figure 3.6 Box and whisker plot of normalised 4-year mean by Mn exposure group (moderate and high) showing median and interquartile ranges, and outliers

(Values for the low exposure group were not available as the residential distance was >10 km from the smelter)

Table 3.5 describes the results from the multivariable linear regression model used to measure the association between Mn exposure and motor outcomes: scores for total PBS, and GP (dominant and non-dominant hand). After adjusting for smoking and alcohol use during pregnancy, gestation, and reaching developmental milestones (in the fully adjusted model), the B coefficients for PBS were 1.64 for both moderate and high exposure, i.e., both groups had a mean PBS score that was almost twice that for the low exposure group. These B coefficients were not significantly different from the low exposure group, although the high exposure group B coefficient was significantly different in the unadjusted model. There was not enough variance to detect a difference in the scores for the PBS test.

There was a positive relationship between Mn exposure and the time taken to complete the grooved pegboard test with the dominant hand for the moderate and high exposure groups (β = 29.71 and 3.55, respectively), but a negative relationship between Mn exposure and the time taken to complete the grooved pegboard test with the non-dominant hand for the high exposure group (-13.17). Again, the differences were not statistically significant.

Table 3.5 Motor outcomes associated with Mn exposure, by exposure group (N=91)

	Unadjusted	Age/sex-adjusted	Fully-adjusted[a]
	β (95% CI)	β (95% CI)	β (95% CI)
Total PBS score[b]			
Low	-	-	-
Moderate	2.21 (0.22, 4.20)	1.92 (-0.72, 3.91)	1.64 (-0.61, 3.73)
High	2.42 (0.50, 4.34)	2.03 (0.14, 3.93)	1.64 (-0.42, 3.68)
Grooved pegboard[c]			
dominant hand			
Low	-	**-**	**-**
Moderate	20.70 (-10.06, 51.47)	23.83 (-8.23, 55.89)	29.71 (-4.27, 63.69)
High	-2.95 (-32.55, 26.64)	1.32 (-29.19, 31.83)	3.55 (-29.70, 36.81)
Non-dominant hand			
Low	**-**	**-**	**-**
Moderate	-0.01 (-43.04, 43.07)	10.08 (-33.77, 53.92)	8.82 (-38.07, 55.70)
High	-16.51 (-57.90, 24.90**)**	-8.97 (-50.70, 32.76)	-13.17 (-59.05,32.71)

PBS=Paediatric Balance Scale; CI= Confidence Interval

[a] Fully adjusted means adjusted for age, sex, mother smoking during pregnancy (yes, no), mother use of alcohol during pregnancy (yes, no), gestation (full term, premature) and developmental milestones (delayed, appropriate, not known)

[b] Poorer motor performance is indicated by a smaller PBS score. The maximum score is 56

[c] Measured time (in seconds). Poorer motor performance is indicated by greater grooved pegboard times

Table 3.6 describes the results from the multivariable linear regression analysis used to measure the association between Mn exposure and cognitive outcomes: visual memory immediate recognition, visual memory delayed recognition, attention/ concentration, and matrix reasoning. As for the motor functions, none of the differences in the mean scores for any of the outcomes was statistically significant in any of the models (unadjusted and adjusted).

Table 3.6 Cognitive outcomes of children associated with Mn exposure by exposure group (N=91)

	Unadjusted	Age/sex-adjusted	Fully-adjusted
	β (95% CI)	**β (95% CI)**	**β (95% CI)**
Visual immediate memory			
Low	-	-	-
Moderate	4.61 (-4.61, 13.82)	4.49 (-4.91, 13.90)	3.70 (-6.92, 14.33)
High	2.97(-5.90, 11.84)	4.27(-4.68, 13.22)	4.84 (-5.55, 15.23
Visual delayed memory			
Low	-	-	-
Moderate	-0.27 (-10.40, 9.85)	-0.01 (-10.66, 10.68)	-0.20 (-12.25, 11.84)
High	2.69 (-7.05, 12.43)	3.33 (-6.83, 13.49)	2.99 (-8.77, 14.77)
Attention/Concentration			
Low	-	-	-
Moderate	-5.45 (-15.16, 4.25)	-6.24 (-15.84, 3.35)	-4.77 (-15.71, 6.17)
High	-6.44 (-15.78, 2.90)	-4.55(-13.68, 4.58)	-2.25 (-12.95, 8.45)
Matrix reasoning			
Low	-	-	-
Moderate	-0.77 (-2.65, 1.09)	-0.99 (-2.94, 0 .95)	-0.87 (-3.07, 1.33)
High	-0.02 (-1.80, 1.76)	-0.01 (-1.80, 1.78)	0.22 (-1.85, 2.29)

Mn=manganese; CI = Confidence Interval

[a] Fully adjusted means adjusted for age, sex, mother smoking during pregnancy (yes, no), mother's use of alcohol during pregnancy (yes, no), mother's level of education (none, grade 1-10, grade 11-12) father's occupation (unemployed, employed, not known).

CHAPTER 4. DISCUSSION

This chapter provides a critical discussion of the findings from the study, which are related to the effect of exposure to ambient Mn on the neurodevelopment of children aged 5-10 years. The findings are discussed according to the objectives of the research and compared to the existing literature discussed in Chapter one.

Description of exposure and demographic characteristics

This cross-sectional study, like several other studies of the same nature,[13,38,41,42,44,54] measured exposure by either mean community Mn concentrations in surface soil and air or with reference to $PM_{2.5}$-Mn, associated with residential proximity to a ferromanganese refinery. The community of interest in this study is exposed to $PM_{2.5}$-Mn at different levels. There was a statistically significant difference in 4-year mean normalised Mn exposure levels between the exposure groups. This indicates that the categorisation into three exposure groups was a valid strategy. All participants spend up to 8 hours a day at the same school which is located within the high exposure area.

The participants were homogenous with regard to race, sex, and home language. This indicates that demographic factors were not confounders in this study. As reported by Tong et al. (2007) and Ronfani (2015), socioeconomic status, maternal level of education and home environment can influence the development of cognitive and motor development.[64,78]

Description of developmental variables

The results regarding gestation, birth weight and reaching developmental milestones, where the premature births (n=4, 36.4%) was the same as low birth weight (n=4, 36.4%) and delayed developmental milestones (n=4, 36.4%,) supports prior knowledge that prematurity and low birth weight are connected.

The employment rate in South Africa decreased to 35.93% in the third quarter of 2021 form 37.73% in the second Quarter.[79] In this community the employment rate of the mothers was below this rate at 30.8% (n=28) and the father's employment rate above the rate at 49.9% (n=45).

Assessment of motor development

We found that motor function, measured as fine motor speed, visual motor integration and balance was not significantly associated with Mn exposure group in this study. A few years ago, Mora et al. (2015) also reported that, in the Salinas Valley in California, US, higher Mn levels were associated with improved motor outcomes in a sample size of 248 (prenatal) and 244 (postnatal) boys.[60] Our study cannot refute this statement as the mean for PBS score was higher (54.15) in the high exposure group than in the moderate exposure group of 53.94 and low (51.72) but, similar to our findings, Parvez et al. (2011) found no associations between Mn and motor function in a sample of 304 children in Bangladesh.[61] Neither did Hernández-Bonilla et al. (2011)[42] find an association between Mn levels (measured in blood) and motor function as assessed by the GP test. However, as discussed earlier, Blood Mn levels are not a good measure of exposure to Mn. The findings of this report are in contrast with the findings of Oulhote et al. (2015), who reported a significant association between Mn exposure through water sources and poorer motor function[40] and studies by Lucchini et al. (2012) that reported higher Mn levels associated with poorer motor coordination and hand dexterity.[54]

Racette et al.'s study on adults in the same geographical area indicated that Mn exposure in South Africa may be associated with clinical parkinsonism.[18] However, the number of adults in that study was much larger (832) and included a comparison group of similar socio-economic status from a non-industrial area.[18]

Although there were no statistically significant differences, there were children that performed below the expected norm, indicating that they had impairment balance skill, this does suggest that children in the area may be impaired with regard to motor development, and that this should be investigated. There might be other factors at play, or the levels of Mn in the 3 groups were not large enough to distinguish differences in motor function. A control group in an area far from the smelter is necessary to test this hypothesis.

Assessment of cognitive development

Assessment of cognitive function, reported as visual immediate memory, visual delayed memory, attention/concentration, and general intelligence, highlighted several areas of concern.

The means of the memory test scores, were more than one standard deviation below the norm in all three exposure groups. This does suggest that children in the area may be impaired with regards to cognitive development, and that this should be investigated.

The overall mean score for the matrix reasoning test was more than one standard deviation below the norm. This indicates impairment of general problem solving and reasoning skills. Again, this should be further investigated in the community.

These findings provide a basis for future research on the effects of environmental Mn exposure on different stages of human development. Information on specific cognitive and motor needs of a population is essential when developing early childhood intervention programmes to target the specific needs of children.

As identified by Leonhard et al.[19] in their systematic review on epidemiological studies of developmental Mn exposure and neurodevelopmental outcomes, only Haynes et al. (2015) have examined the association between Mn in hair and working memory; they also reported no statistically significant differences in Mn in hair between exposure categories.[41] Mora et al. (2015) also reported associations with working memory that were not statistically significant, using prenatal dentin Mn as a measure of exposure.[60]

Investigation into association

Similar to other studies, [60,61] we did not find significant associations between levels of Mn exposure and motor function.

Two studies reported significant associations between Mn exposure and cognitive outcomes. The first, by Haynes et.al (2015), investigated Mn exposure and neuro-cognitive outcomes in rural school-aged children in Ohio. They included 404 participants and used biomarkers from blood and hair samples.[41] The second study,

by Carvalho et al. (2018), included fewer participants (n=70) and used biomarkers from hair samples. They studied environmental manganese exposure and associations with memory, executive function, and hyperactivity in Brazilian children.[38] However, our investigation into the association between Mn exposure levels and neurodevelopmental outcomes concluded, like other studies, [12,60,61] that there was a nonsignificant relationship between Mn exposure and neurodevelopmental outcomes.

Children participating in our study struggled with cognitive tasks. If the results from this study can be compared to those conducted in an area with no sources of Mn exposure, using the same test battery, the potential association with Mn exposure can be investigated more robustly.

This study expands on information and knowledge gained from previous research on environmental Mn exposure in adults in this community (Racette et al.) (2022),[17,18] but in a different age group, namely children aged 5 - 10 years. The findings from the study can be added to already published research, to further justify the development and implementation of policies to reduce Mn emissions from ferro-manganese smelters. They can also be used for future research and discussions on the effect of exposure to environmental Mn in a wider age band.

Findings from this and similar research can assist academics and other key stakeholders to promote programmes and policies to reduce exposure to Mn and/or alleviate the negative health effects of cumulative Mn exposure. In addition, the findings provide valuable information for stakeholders to further the campaign to spread awareness on healthy living choices and to improve general wellbeing in the community.

Other factors that affect children's motor and cognitive function

Child development is influenced by multiple and widespread factors, some of which have direct links to the environmental exposure to different heavy metals. Other potential risk factors are related to genetic and epigenetic factors and the social economic environment, including education.

Studies have described the presence of a gene mutation when an individual has been exposed to Mn over time.[80] Prenatal aspects such as mother's diet, stress levels and exposure to smoke and alcohol[78,81] play important roles in in-utero development. The stimulation of the child during the first 1 000 days of life[82,83] affects its ability to engage with the teacher and environment, at the stage when formal education starts.

Benefits of the study to the community

The school community benefited from this study as it has created interest and awareness about industrial exposures, in general, and Mn exposure, specifically. In addition, Sicelo Primary School is now on the list of beneficiaries of corporate community improvement projects by Pick and Pay overseen by Actu8. Selected families regularly receive food hampers from the Pick and Pay Feed the Nation initiative.[84] The school has also been incorporated into the Pick and Pay school club[85] and, consequently, is provided with additional teaching aids and material that directly benefit the children, their educational development, and their families'.



Figure 4.1 Corporate involvement at the school as result of the study

Limitations

Adequate recruitment was key to the success of this study. Access to the learners at the school was simple, but contacting the parent or guardian to obtain consent and complete the interviewer-administered questionnaire proved to be difficult. Telephone numbers were often incorrect, and appointments were not kept.

The COVID-19 pandemic limited access to learners for prolonged periods of time. This limited the number of learners that were enrolled, thereby reducing the power of the study.

Precise geocoding for each location was not available because of safety concerns. Many of the learners reside in informal settlements, which were not easily accessible or safe for the investigator to visit to record the exact location by geocode of each residence. Thus, the investigator had to match each address to the closest coded residence available from Racette et al.'s study.[17,18,31]

Samples were not collected from the learners for biomarker analysis. Data from environmental measurements are often validated by biomarkers in hair,[12,37,42,45,52,54] nails[61] and/or blood.[42,54,61] It is postulated that environmental measurements need to be validated against individual measurements. Aschner and Aschner (2005) reported that environmental estimates of Mn exposure are likely not to reflect internal Mn dose due to other sources of Mn such as diet and assimilation rate.[86]

The Mn exposures were estimated and the exposures in the three groups might have been homogenous in this regard, invalidating the comparisons across the groups. In contrast with studies of similar sample sizes,[12,42,54] we did not have a control group with no Mn exposure.

There was limited Wi-Fi access at the school, as in most areas of similar socio-economic status in South Africa. Therefore, although the questionnaire was designed in RedCap, data were collected on paper-based data capture sheets. Low technology test materials work most efficiently in these areas.

Ethical Considerations

The investigator met with the principal and the chairperson of the School Governing Body. They were provided with information sheets (Appendix G and H). After several delays, permission was obtained to conduct the study by the Gauteng Department of Education.

Ethical approval for the study was obtained from the University of the Witwatersrand Human Research Ethics Committee (HREC): ethics clearance certificate no. M190853 (Appendix I).

The research was completed with full knowledge of, consent, and support from the principal of Sicelo Primary School and the School Governing Body and all steps were taken to conform to the Protection of Personal Information (POPI) Act.[87]

Written informed parental consent (Appendix E) and child assent (Appendix F) were obtained before commencement of the study. Consent for taking, and use of photographs, was obtained (Appendix J).

Hard copies of assessment materials and raw data are stored in a locked cabinet and will be kept until the participants turn 21, after which they will be destroyed.

If, during the assessment, a child was identified as needing further medical or allied medical investigation, the recommendation to take the child to the local clinic was made at the same meeting, and referral was made to the nearest clinic. Advice in accordance with the scope of practice of an Occupational Therapist and that relates to functional skills was made after the assessment at the same appointment. Advice was given to the parents/guardians to assist them to manage their children's learning experiences. This was in the form of activity ideas to assist the child at home.

The investigator was trained to administer the specific tests and is qualified and trained to conduct assessments of a standardised nature. The investigator had access to training and supervision to ensure competence in collecting the data needed.

Recommendations

A study using the same methodology should be conducted in an area where there is no industrial pollution. The findings from such a study can be used as a comparison for the findings from this study.

Biomarkers should be collected to evaluate exposure to Mn more accurately. Residual analysis, which was not done in our statistical analysis, should be conducted to check if the regression models that we developed were predicting in a linear way.

The information from this study can be used to promote community and corporate involvement - to motivate for the development of a non-profit, non-governmental organisation to assist with community stimulation programmes, focussing on development areas highlighted in this study. This initiative could also support mothers with training and employment opportunities.

Conclusion

This study laid a foundation in neurodevelopmental testing of children in a Mn exposed community. The findings are in line with those from previous similar studies, in that no significant associations between exposure and either motor or cognitive outcomes were identified. Further research, using larger sample sizes, and including unexposed comparison groups should be conducted.

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Appendix A: Plagiarism Declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Annemarie McGovan (Student number: 1308737) am a student registered for the degree of MSc Med - Exposure Science in the academic year 2018.

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.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: AMcGovan Date: 31 March 2022

Appendix B: Test battery

A

PEDIATRIC BALANCE SCALE

Name: _____ Date: _____

Location: _____ Examiner: _____

Item Description	Score *0 - 4*	Seconds *optional*
1. Sitting to standing	_____	
2. Standing to sitting	_____	
3. Transfers	_____	
4. Standing unsupported	_____	_____
5. Sitting unsupported	_____	_____
6. Standing with eyes closed	_____	_____
7. Standing with feet together	_____	_____
8. Standing with one foot in front	_____	_____
9. Standing on one foot	_____	_____
10. Turning 360 degrees	_____	_____
11. Turning to look behind	_____	_____
12. Retrieving object from floor	_____	
13. Placing alternate foot on stool	_____	
14. Reaching forward with outstretched arm	_____	_____
Total Test Score	_____	

General Instructions

1. Demonstrate each task and give instructions as written. A child may receive a practice trial on each item. If the child is unable to complete the task based on their ability to understand the directions, a second practice trial may be given. Verbal and visual directions may be clarified through the use of physical prompts.

2. Each item should be scored utilizing the 0 to 4 scale. Multiple trials are allowed on many of the items. The child's performance should be scored based upon the lowest criteria, which describes the child's best performance. If on the first trial a child receives the maximal score of 4, additional trials need not be administered. Several items require the child to maintain a given position for a specific time. Progressively, more points are deducted if the time or distance requirements are not met; if the subject's performance warrants supervision; or if the subject touches an external support or receives assistance from the examiner. Subjects should understand that they must maintain their balance while attempting the tasks. The choice, of which leg stand on or how far to reach, is left to the subject. Poor judgement will adversely influence the performance and the scoring. In addition to scoring items 4, 5, 6, 7, 8, 9, 10, and 13, the examiner may choose to record the exact time in seconds.

Figure. No caption available.

PBS item description with scoring criteria

Item description	Scoring criteria: Best of three trials
1. Sitting to standing	4: able to stand without using hands and stabilise independently. 3: able to stand independently using hands. 2: able to stand using hands after several tries. 1: needs minimal assist to stand or to stabilise. 0: needs moderate or maximal assist to stand.
2. Standing to sitting	4: sits safely with minimal use of hands. 3: controls descent by using hands. 2: uses back of legs against chair to control descent. 1: sits independently, but has an uncontrolled descent 0: needs assistance to sit
3. Transfers	4: able to transfer safely with minor use of hands 3: able to transfer safely; definite need of hands 2: able to transfer with verbal cueing and /or supervision 1: needs one person to assist 0: needs two people to assist or supervise (close guard) to be safe
4. Standing unsupported	4: able to stand safely 30 seconds 3: able to stand 30 seconds with supervision (spotting) 2: able to stand 15 seconds unsupported 1: needs several tries to stand 10 seconds unsupported 0: unable to stand 10 seconds unassisted
5. Sitting unsupported	4: able to sit safely and securely 30 seconds 3: able to sit 30 seconds under supervision or may require definite use of upper extremities to maintain sitting position 2: able to sit 15 seconds 1: able to sit 10 seconds 0: unable to sit 10 seconds without support
6. Standing with eyes closed	4: able to stand 10 seconds safely

	3: able to stand 10 seconds with supervision 2: able to stand 3 seconds 1: unable to keep eyes closed 3 seconds but stays steady 0: needs help to keep from falling
7. Standing with feet together	4: able to place feet together independently and stand 30 seconds safely 3: able to place feet together independently and stand for 30 seconds with supervision 2: able to place feet together independently and stand for 30 seconds 1: needs help to attain position but able to stand 30 seconds with feet together 0: needs help to attain position and/or unable to hold for 30 seconds
8. Standing with one foot in front	4: able to place feet tandem independently and hold 30 seconds 3: able to place foot ahead of other independently and hold 30 seconds. 2: able to take small step independently and hold 30 seconds, or required assistance 1: needs help to step but can hold 15 seconds. 0: loses balance while stepping or standing
9. Standing on one foot	4: able to lift leg independently and hold 10 seconds. 3: able to lift leg independently and hold 5 to 9 seconds. 2: able to lift leg independently and hold 3 to 4 seconds. 1: tries to lift leg; unable to hold 3 seconds but remains standing. 0: unable to try or needs assistance to prevent fall.
10. Turning 360 degrees	4: able to turn 360 degrees safely in 4 seconds or less each way. 3: able to turn 360 degrees safely in one direction only in 4 seconds or less. 2: able to turn 360 degrees safely but slowly. 1: needs close supervision or constant verbal cueing. 0: needs assistance while turning.

11. Turning to look behind	4: looks behind/ over each shoulder; weight shifts include trunk rotation. 3: looks behind/ over shoulder with trunk rotation, weight shift in the opposite direction is to the level of the shoulder, no trunk rotation. 2: turns head to look to level of shoulder; no trunk rotation. 1: needs supervision when turning; chin moves greater than half the distance to the shoulder. 0: needs assist to keep from losing balance or falling.
12. Retrieving object from floor	4: able to pick up an object safely and easily. 3: able to pick up object but needs supervision. 2: unable to pick up object but reaches 1 to 2 inches from object and keeps balance independently. 1: unable to pick up object; needs supervision while attempting. 0: unable to try, needs assist to keep from losing balance or falling.
13. Placing alternate foot on stool	4: stands independently and safely and completes 8 steps in 20 seconds. 3: able to stand independently and complete 8 steps > 20 seconds. 2: able to complete 4 steps without assistance but requires close supervision. 1: able to complete 2 steps; needs minimal assistance. 0: needs assistance to maintain balance or keep from falling.
14. Reaching forward with outstretched arm	4: can reach forward confidently > 10 inches 3: can reach forward > 5 inches, safely 2: can reach forward > 2 inches, safely. 1: reaches forward but needs supervision. 0: loses balance while trying, requires external support.

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Washington University in St. Louis School of Medicine

GROOVED PEGBOARD

WITS UNIVERSITY

Subject ID: _____ **Examiner's Initials:** _____

Visit Date: ☐☐ Day ☐☐☐ Month (e.g. FEB) ☐☐☐☐ Year

The Grooved Pegboard is a manipulative dexterity test. This unit consists of 25 holes with randomly positioned slots. Pegs, which have a key along one side, must be rotated to match the hole before they can be inserted. For the test, the pegboard should be placed in mid-line with the participant so that the board is at the edge of the table and the peg tray is immediately above the board

General Directions: For the right- hand trial, the examiner demonstrates that the pegs are placed from participant's *left to right*, and from *right to left* for the left hand trial. The dominant hand trial is administered first, followed by the non-dominant hand trial. The examiner encourages the participant to perform the task as quickly as possible, telling him or her to speed up if necessary. The pegs must be put in the board in the exact order and in the correct direction.

Item Instructions:

Say to Participant... **This is a pegboard and these are the pegs**. (Examiner points out each and then picks up one of the pegs and continues.) **All the pegs are the same. They have a groove, that is, a round side and a square side and so do the holes in the boards. What you must do is match the groove of the peg with the groove of the board and put these pegs into the holes like this.** (The examiner demonstrates by filling the top row. Remove the pegs, putting them back into the tray.)
When I say go, begin here and put the pegs into the boards as fast as you can, using only your (dominant) hand. Fill the top row completely from this side to this side. For the right hand trial, the examiner demonstrates that the pegs are placed from participant's left to right, and from right to left for the left hand trial. **Do not skip any; fill each row the same way you filled the top row. Any questions? Ready, as fast as you can, go.**

Supplementary Instructions:

- A trial may be discontinued after 5 minutes. The difficulty should be described in the notes section on this form and the test will be noted as incomplete
- **Record** the length of time required to perform each trial beginning when the participant starts the task until the last peg is put in, or if the test is discontinued
- **Record** the number of "drops" made during each trial. A "drop" is any unintentional drop of a peg. If a peg is intentionally laid down on the side of the tray or table, in order to purposefully manipulate the peg, it is not considered a drop
- **Record** the number of pegs correctly placed in the holes for each trial (this number will be 25 if not discontinued)
- If a peg is turned with the hand not being tested, it should be noted on this form
- **Only one peg** is to be picked up at a time and the participant should immediately be told if more than one is picked up. Also, only one hand is to be used.
- **Any factor that** may affect the participant's performance **should be noted,** e.g. sore finger, bandage, etc.
- If a peg is dropped to the floor, the examiner should not make an attempt to pick it up during the trial.

DISCONTINUE RULE
After 5 minutes

SCORING
Record: time to complete trial, drops, pegs placed

Handedness: _____

Hand	Left	Right
Time per Hand:	____ : ____ , ____ minutes seconds milliseconds	____ : ____ , ____ minutes seconds milliseconds
# of Dropped Pegs per Hand:	_____ drops	_____ drops
# of Placed Pegs per hand: (this # will be 25 unless testing was stopped after 5 minutes before the task was completed)	_____ pegs	_____ pegs
Was trial discontinued after 5 minutes? (circle Yes or No)	Yes No	Yes No
Number of times non-testing hand was used:	_____	_____
Notes:		

CMS Children's Memory Scale
Morris J. Cohen

Record Form Ages 5–8

Core Battery Summary Page
Refer to Chapter 3 in your Manual for complete instructions on filling out the Summary information.

Child's Name _____ Sex _____
School _____ Grade _____
Teacher _____ Handedness _____
Examiner _____

	Year	Month	Day
Date Tested			
Date of Birth			
Age			

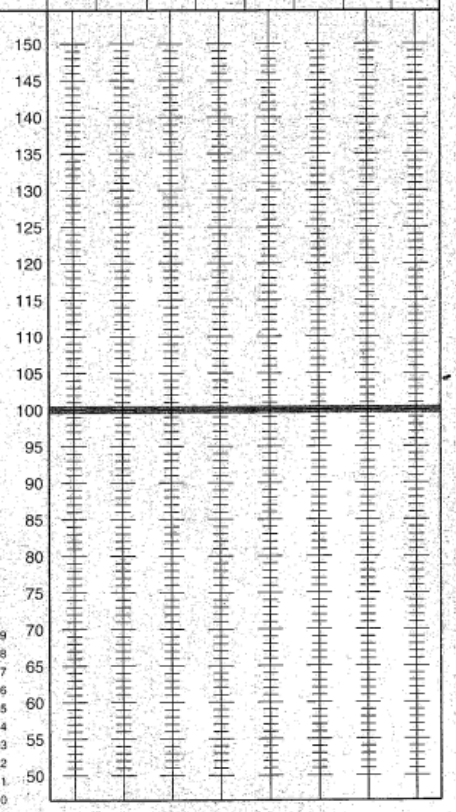
Reason for Referral _____
Behavioral Observations _____

Core Subtest Scores	Raw Score	Scaled Score (SS)							%tile Rank
Dot Locations									
Learning									
Total Score									
Long Delay									
Stories									
Immediate									
Delayed									
Delayed Recog									
Faces									
Immediate									
Delayed									
Word Pairs									
Learning									
Total Score									
Long Delay									
Delayed Recog									
Numbers									
Total Score									
Sequences									
Total Score									
Sum of SS									
		Vis Imm	Vis Del	Ver Imm	Ver Del	Attn/ Conc	Learn	Del Rec	

↓ + ↓ + ↓ + ↓

General Memory (Sum of Scaled Scores)

Index Scores	Vis Imm	Vis Del	Ver Imm	Ver Del	Gen Mem	Attn/ Conc	Learn	Del Rec
Sum of Subtest Scaled Scores								
Index Score								
Conf Interval Level ___%								
Percentile Rank								



	Visual Memory				Verbal Memory						Attention/ Concentration		Learning	
	Immediate		Delayed		Immediate		Delayed		Delayed Rec					
	Dot Loc TS	Faces Imm	Dot Loc Lng Del	Faces Del	Stories Imm	Wrd Prs TS	Stories Del	Wrd Prs Lng Del	Stories Del Rec	Wrd Prs Del Rec	Num TS	Seq TS	Dot Loc Learn	Wrd Prs Learn
19	•	•	•	•	•	•	•	•	•	•	•	•	•	•
18	•	•	•	•	•	•	•	•	•	•	•	•	•	•
17	•	•	•	•	•	•	•	•	•	•	•	•	•	•
16	•	•	•	•	•	•	•	•	•	•	•	•	•	•
15	•	•	•	•	•	•	•	•	•	•	•	•	•	•
14	•	•	•	•	•	•	•	•	•	•	•	•	•	•
13	•	•	•	•	•	•	•	•	•	•	•	•	•	•
12	•	•	•	•	•	•	•	•	•	•	•	•	•	•
11	•	•	•	•	•	•	•	•	•	•	•	•	•	•
10														
9	•	•	•	•	•	•	•	•	•	•	•	•	•	•
8	•	•	•	•	•	•	•	•	•	•	•	•	•	•
7	•	•	•	•	•	•	•	•	•	•	•	•	•	•
6	•	•	•	•	•	•	•	•	•	•	•	•	•	•
5	•	•	•	•	•	•	•	•	•	•	•	•	•	•
4	•	•	•	•	•	•	•	•	•	•	•	•	•	•
3	•	•	•	•	•	•	•	•	•	•	•	•	•	•
2	•	•	•	•	•	•	•	•	•	•	•	•	•	•
1	•	•	•	•	•	•	•	•	•	•	•	•	•	•

PEARSON PsychCorp

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Product Number 0154038016

CMS RECORD SHEET

Age: 9-16

IDENTIFYING INFORMATION

Name:	Female / Male	Grade:

	Year	Month	Day
Date Tested			
Date of Birth			
Age*			

*Do not round up

Glasses: Y / N Type: _____	Handedness: L / R Other: _____
Examiner's name:	

SUMMARY OF SCORES

Subtest		Raw Score	Scaled Score	Descriptive Term						
				1-3	4-5	6-7	8-12	13-14	15-16	17-20
Dot Location	Learn									
	Short									
	TOTAL									
• Dot Location 2										
Number TS	Forward									
	Backward									
	TOTAL									
Sequence TS										
Family Pictures										
• Family Pictures 2										
Faces	1									
	2									

DESCRIPTIVE TERMS

1-3	4-5	6-7	8-12	13-14	15-16	17-20
Very Poor	Poor	Below Average	Average	Above Average	Superior	Very Superior
<70	70-79	80-89	90-110	111-120	121-130	>130

LEARNING CURVE ANALYSIS

Dot Location – Ages 9-12

RAW SCORE	1	2	3	IR
8				
7				
6				
5				
4				
3				
2				
1				
TRIAL				

COMPOSITE SCORES	RS	SS
Attention & Concentration		
Visual Immediate		
Visual Delayed		

COMMENTS

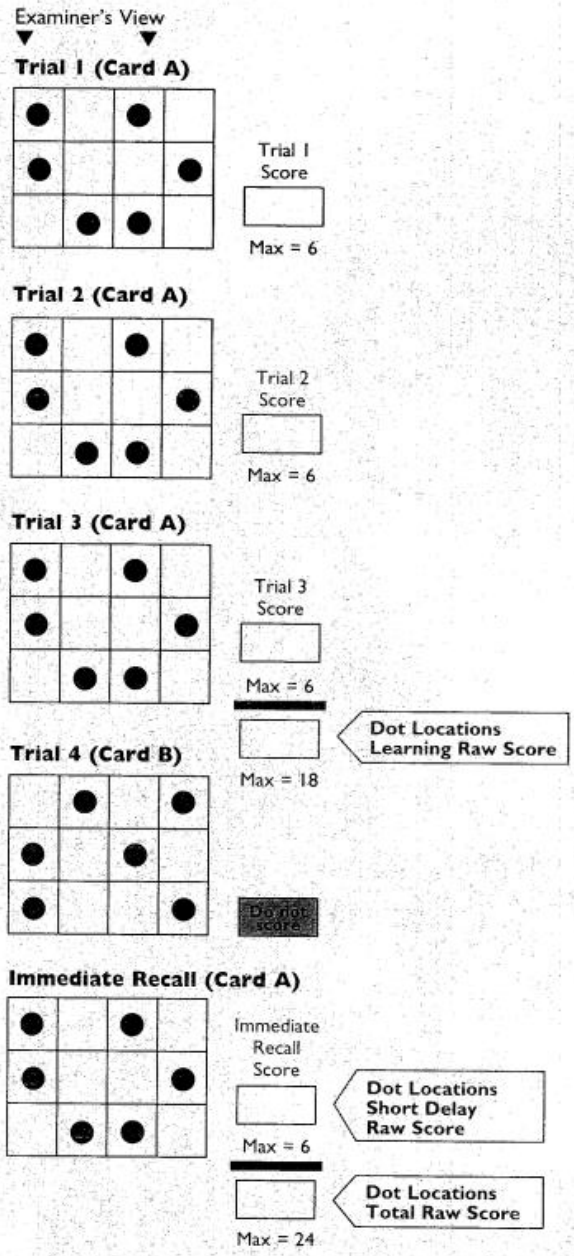
Dot Location – Normative Table

	Age									
Trial	5	6	7	8	9	10	11	12	13-14	15-16
1	4	4	5	5	5	6	6	6	6	6
2	4	5	5	5	6	6	7	7	7	7
3	4	5	5	6	7	7	7	7	7	7
IR	4	4	5	5	6	6	6	7	7	7

7. Dot Locations

For each trial and Immediate Recall, mark an *X* on the grid to indicate the placement (correct and incorrect) of each chip. (Grids are shown from examiner's view.)

Trial Scores: Total the number of correctly placed chips for each of Trials 1–3 and Immediate Recall. Score one point for each.
Correct chip placements are indicated by black dots. Note. Trial 4 is not scored.
Dot Locations Learning Raw Score: Add the scores for Trials 1–3.
Dot Locations Short Delay Raw Score: Equivalent to the Immediate Recall Score.
Dot Locations Total Raw Score: Add the Dot Locations Learning Raw Score and the Dot Locations Immediate Recall Raw Score.



7. Numbers

Discontinue after scores of 0 on both trials of an item.

Record verbatim the response for each item. Score 1 point for each correctly recalled sequence. Score 0 points for each incorrectly recalled sequence.

Numbers Forward Raw Score: Add the scores for Forward Items 1–8.
Numbers Backward Raw Score: Add the scores for Backward Items 1–7.
Numbers Total Raw Score: Add the Numbers Forward Raw Score and the Numbers Backward Raw Score.

Forward

Item	Response	Score 0 or 1
1. Trial 1 3–5		
Trial 2 7–2		
2. Trial 1 2–8–6		
Trial 2 6–3–4		
3. Trial 1 6–2–5–8		
Trial 2 2–4–1–7		
4. Trial 1 9–5–1–4–8		
Trial 2 5–8–2–1–6		
5. Trial 1 4–7–8–1–6–3		
Trial 2 7–3–9–8–6–4		
6. Trial 1 6–1–7–4–2–3–8		
Trial 2 9–3–8–6–5–1–2		
7. Trial 1 5–3–8–7–2–1–6–4		
Trial 2 2–4–9–5–7–1–6–3		
8. Trial 1 1–6–4–5–9–7–2–8–3		
Trial 2 4–5–2–3–6–8–9–7–1		

Numbers Forward Raw Score ____

Max = 16

Backward

Item	Correct Response	Response	Score 0 or 1
1. Trial 1 3–8	8–3		
Trial 2 7–4	4–7		
2. Trial 1 4–8–3	3–8–4		
Trial 2 3–6–8	8–6–3		
3. Trial 1 5–2–9–6	6–9–2–5		
Trial 2 8–3–4–9	9–4–3–8		
4. Trial 1 4–7–1–5–3	3–5–1–7–4		
Trial 2 9–2–7–5–8	8–5–7–2–9		
5. Trial 1 1–8–6–9–5–2	2–5–9–6–8–1		
Trial 2 3–4–6–9–7–1	1–7–9–6–4–3		
6. Trial 1 8–2–5–4–9–3–2	2–3–9–4–5–2–8		
Trial 2 4–1–5–8–7–2–9	9–2–7–8–5–1–4		
7. Trial 1 6–8–9–5–1–2–6–3	3–6–2–1–5–9–8–6		
Trial 2 3–2–1–8–7–5–9–4	4–9–5–7–8–1–2–3		

Numbers Backward Raw Score ____

Max = 14

Numbers Total Raw Score ____

Max = 30

8. Sequences

Discontinue after 4 consecutive scores of 0.

For each item, cross out any elements omitted and write in any elements said in the wrong sequence. Record the response time in seconds and circle the number of errors. If examinee makes an error within a sequence, but subsequent responses are consistent with the new sequence, this counts as only one error.

For each item, circle the Accuracy Score that corresponds to the number of errors. Circle an Accuracy Score of 0 if examinee does not attempt or complete an item. If an item has an Accuracy Score of 3 points, also circle the number of Bonus Points that corresponds to the response time.

Item Scores: Add the Accuracy Score and the Bonus Points (if applicable) for each item.
Sequences Total Raw Score: Add the scores for Items 1–12.

	Item/Correct Response/Response	Response Time	Number of Errors	Accuracy Score	+ Bonus Points =	Item Score
1–10	1. 1 2 3 4 5 6 7 8 9 10		3+ 2 1 0	0 1 2 3	5+" 3–4" 2" 1" 1 2 3 4	
Alphabet	2. A B C D E F G H I J K L M N O P Q R S T U V W X Y Z		3+ 2 1 0	0 1 2 3	9+" 6–8" 4–5" 1–3" 1 2 3 4	
Days	3. Sunday Monday Tuesday Wednesday Thursday Friday Saturday		3+ 2 1 0	0 1 2 3	4+" 3" 2" 1" 1 2 3 4	
10–1	4. 10 9 8 7 6 5 4 3 2 1		3+ 2 1 0	0 1 2 3	4+" 3" 2" 1" 1 2 3 4	
20–1	5. 20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1		3+ 2 1 0	0 1 2 3	8+" 5–7" 4" 1–3" 1 2 3 4	
Days Backward	6. Sunday Saturday Friday Thursday Wednesday Tuesday Monday		3+ 2 1 0	0 1 2 3	14+" 8–13" 6–7" 1–5" 1 2 3 4	
Months	7. January February March April May June July August September October November December		3+ 2 1 0	0 1 2 3	8+" 5–7" 4" 1–3" 1 2 3 4	
Odds 1–15	8. 1 3 5 7 9 11 13 15		3+ 2 1 0	0 1 2 3	13+" 8–12" 7" 1–6" 1 2 3 4	
4s	9. 0 4 8 12 16 20 24 28 32 36 40		3+ 2 1 0	0 1 2 3	22+" 14–21" 9–13" 1–8" 1 2 3 4	
6s	10. 0 6 12 18 24 30 36 42 48 54 60		3+ 2 1 0	0 1 2 3	29+" 19–28" 13–18" 1–12" 1 2 3 4	
Months Backward	11. December November October September August July June May April March February January		3+ 2 1 0	0 1 2 3	31+" 22–30" 14–21" 1–13" 1 2 3 4	
Letters/Numbers	12. A1 B2 C3 D4 E5 F6 G7 H8 I9 J10 K11 L12 M13 N14 O15 P16 Q17 R18 S19 T20 U21 V22 W23 X24 Y25 Z26		3+ 2 1 0	0 1 2 3	99+" 70–98" 51–69" 1–50" 1 2 3 4	

Sequences Total Raw Score ____ Max = 84

3. Faces

For each item, circle Y (Yes) or N (No) to indicate examinee's response.

Score 1 point for each correct response and 0 points for each incorrect response. Correct responses are indicated in *color type*.

Faces Immediate Raw Score: Add the scores for Items 1–36.

Item/Response	Score 0 or 1
1. Y *N*	
2. *Y* N	
3. Y *N*	
4. *Y* N	
5. *Y* N	
6. Y *N*	
7. Y *N*	
8. *Y* N	
9. *Y* N	
10. Y *N*	
11. *Y* N	
12. Y *N*	
13. *Y* N	
14. *Y* N	
15. Y *N*	
16. Y *N*	
17. *Y* N	
18. *Y* N	
19. Y *N*	
20. *Y* N	
21. *Y* N	
22. Y *N*	
23. *Y* N	
24. *Y* N	
25. Y *N*	
26. Y *N*	
27. *Y* N	
28. Y *N*	
29. *Y* N	
30. Y *N*	
31. Y *N*	
32. *Y* N	
33. Y *N*	
34. Y *N*	
35. *Y* N	
36. Y *N*	

Faces Immediate Raw Score ____ Max = 36

12. Faces 2

For each item, circle Y (Yes) or N (No) to indicate examinee's response.

Score 1 point for each correct response and 0 points for each incorrect response. Correct responses are indicated in *color type*.

Faces Delayed Raw Score: Add the scores for Items 1–36.

Item/Response	Score 0 or 1
1. Y *N*	
2. Y *N*	
3. *Y* N	
4. Y *N*	
5. *Y* N	
6. Y *N*	
7. Y *N*	
8. *Y* N	
9. Y *N*	
10. Y *N*	
11. *Y* N	
12. *Y* N	
13. *Y* N	
14. Y *N*	
15. Y *N*	
16. Y *N*	
17. *Y* N	
18. Y *N*	
19. *Y* N	
20. *Y* N	
21. Y *N*	
22. *Y* N	
23. Y *N*	
24. *Y* N	
25. *Y* N	
26. *Y* N	
27. Y *N*	
28. *Y* N	
29. Y *N*	
30. *Y* N	
31. Y *N*	
32. *Y* N	
33. *Y* N	
34. Y *N*	
35. Y *N*	
36. *Y* N	

Faces Delayed Raw Score ____ Max = 36

10. Dot Locations 2

Mark an *X* on the grid to indicate the placement (correct and incorrect) of each chip. (Grids are shown from examiner's view.)

Dot Locations Long Delay Raw Score: Total the number of correctly placed chips. Score one point for each. Correct chip placements are indicated by black dots.

Examiner's View

Dot Locations Long Delay Raw Score ____ Max = 6

MATRIX REASONING scoring form

Subject ID: _____ **Examiner 's Initials _____**

Date: _____

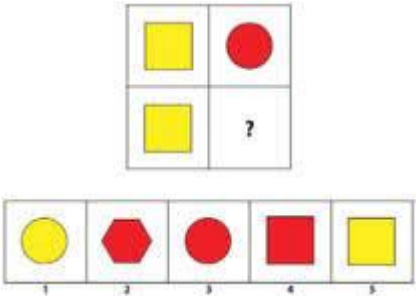
Test Start Time: _____ **Test Finish Time: _____**

Start Age 6-8: Samples A-C then Item 4. Age 9-11: Samples A-C then Item 7. Reverse Ages 6-16: Score of 0 on either of the first two items given, administer preceding items in reverse order until two consecutive perfect scores are obtained. Discontinue after 4 consecutive scores of 0 or 4 scores of 0 on five consecutive items.

ITEM	RESPONSE OPTIONS					SCORE (0 or 1	COMMENTS
A	**1**	2	3	4	5		
B	1	2	3	4	**5**		
C	1	2	3	**4**	5		
1	1	**2**	3	4	5		
2	1	2	**3**	4	5		
3	1	2	3	**4**	5		
4	1	**2**	3	4	5		
5	1	2	3	4	**5**		
6	**1**	2	3	4	5		
7	1	2	3	**4**	5		
8	1	**2**	3	4	5		
9	1	2	3	**4**	5		
10	1	2	**3**	4	5		
11	1	2	3	4	**5**		
12	**1**	2	3	4	5		
13	**1**	2	3	4	5		
14	1	2	3	**4**	5		
15	**1**	2	3	4	5		
16	1	**2**	3	4	5		
17	1	**2**	3	4	5		
18	1	2	3	**4**	5		
19	1	2	3	4	**5**		
20	1	2	3	**4**	5		
21	1	2	**3**	4	5		
22	1	2	**3**	4	5		
23	1	2	3	4	**5**		
24	1	2	3	**4**	5		
25	1	2	**3**	4	5		
26	1	**2**	3	4	5		
27	**1**	2	3	4	5		
28	**1**	2	3	4	5		
29	1	**2**	3	4	5		
30	1	**2**	3	4	5		
31	1	2	3	4	**5**		
32	1	2	**3**	4	5		
33	1	2	3	**4**	5		
34	**1**	2	3	4	5		
35	1	2	3	4	**5**		

Matrix Reasoning (MR)

• The child views an incomplete matrix or series and selects the response option that completes the matrix or series.



• Materials

– Administration and Scoring Manual

– Record Form

– Stimulus Book 1 MR Start Points

• Start

– Ages 6–8: Sample Items A & B, then Item 1

– Ages 9–11: Sample Items A & B, then Item 5

– Ages 12–16: Sample Items A & B, then Item 9

– Use clinical judgment to start with Sample Items A & B, then Item 1, regardless of age.

• Reverse

– If a child aged 9–16 does not obtain a perfect score on either of the first two items given, administer the preceding items in reverse order until the child obtains perfect scores on two consecutive items.

• Discontinue

– Discontinue after 4 consecutive scores of 0.

Appendix C: Questionnaire

To be completed by investigator.

Participant number: _____ Examiner's Initials: _____

Visit Date: _____

Day Month Year

Contact number of Guardian/Parent: #1: _____

#2: _____

Demographic Information

Interview completed with: Mother: _____Father: _____ Other (name)_____

Age of participant: _____

Gender: Male _____ Female _____Home language: _____

Second language: _____

Race: White ___ Black____ Asian ____ Coloured _____

Mother's highest level of education (highest grade completed):

_____

Mother's occupation:

_____

Father's occupation:

_____

Family structure: (extended family residing together, number of siblings)

_____

_____

_____

_____

Head of household relationship to child (father, mother, uncle, brother)

_____. How old is the head of the household? _____

Background information

Were there any complications like high blood pressure or diabetes during pregnancy? (If yes please elaborate).

_____

_____

_____

Age of mother when baby was born:

_____

Age of father when baby was born:

_____

Did the mother smoke tobacco (cigarettes or pipe) during pregnancy? Y____ N____

If yes…. How much did she smoke on average? Number of cigarettes per week _____

Was she regularly exposed to tobacco smoke during pregnancy? (Did the Father smoke or any other family members in your presence during pregnancy?)

_____

_____

_____

Did the mother drink alcohol during pregnancy? Y_____ N_____

If yes…. How much on average? Beer: _____

Wine: _____

Spirits: _____

Other (specify): _____

Birth history

Full term: _____ or Premature: _____ (name weeks of gestation)

Vaginal birth: _____ with instruments: _____ Bridge: _____

Caesarean planned: _____ emergency:
_____(reason)

Weight at birth: _____

Duration of hospitalisation after birth: _____ Reason:
_____

Were there any complications during birth? Y_____ N_____

If yes…. please provide more details:

_____

_____

Developmental history

As baby (0 to 12 months) was your child breastfed _____ (until which age?)
Formula: _____

Did your baby have any feeding related difficulties i.e., reflux, cramps, colic?

_____

_____

_____

Was your baby hospitalised? Y_____ N_____

If yes…. Why?

_____

At what age (months) did your child:

Roll over: _____ Sit: _____

Crawl: _____ Walk: _____Say first word:
_____

Medical History

Has your child had any of the following childhood illnesses?

Chicken pocks _____ Measles_____ Mumps _____Other: _____(name)

Has your child ever had fever fits? _____ If yes, when? _____

Does your child suffer from any allergies? _____

Specify and what type of medication do they use?

_____

_____

Operations:

Name/ type of Operation	Body part	Year of Operation

Hopitalisation:

Reason	Duration	Age of child / year

Diseases or conditions that your child receives treatment for (i.e., ADD, epilepsy, diabetes, cancer, autism):

Name of condition	Year diagnosed

Chronic medication:

Medication	**Purpose or reason for medication**	**How long has child been taking the medication**

Education History

Grade	Year	School
R		
1		
2		
3		
4		
5		

Complete Residential History

Please start with your current address and work backwards (indicate where the child has lived with you and not, indicate where he/she stayed.)

Address ***If your child did not reside with you, please indicate below the address where they resided and with whom***	***Province***	***Child living at that address ✓/ x***	***Date started (month/yr.)***	***Date ended (month/yr.)***

Appendix D: Information Letter

THE EFFECT OF EXPOSURE TO ENVIRONMENTAL MANGANESE ON NEUROBEHAVIOURAL FUNCTION OF CHILDREN AGED 5 TO 10 IN MEYERTON, SOUTH AFRICA

Dear Sir/Madam

Thank you for taking the time to read this letter. My name is Annemarie McGovan, and I am a student at the University of the Witwatersrand. I am doing research as a requirement for a master's degree.
The purpose of this study is to assess the effect of Manganese in the air on children's cognitive and motor development.
I have sent you this letter because your child has been chosen to be in the study. If you and your child agree to participate, you will be asked to complete a questionnaire and your child will be asked to do some tests. I would like to test how your child's thinking and moving is developing.

All this will be done at Sicelo Primary School at a time that is convenient for you (after school, on a weekend, or in the school holidays). You do not have to take part, and if you both decide to participate, you can stop at any time during the tests, with no consequences to you or your child.
Nobody will know what you answered or how your child did in the tests. The information will not be shared with anybody. Whatever your decision is to – participate or not – it will have no effect on your child's marks at school.

The following will be expected of you and your child:

1. You will be asked to complete a questionnaire about where you live, your health and your child's health. This will take about 30 minutes.
2. Your child will be asked to do the following tests:
    - Two motor coordination tests: 1 balance and 1 fine motor and dexterity test (How your child moves.)
    - A general cognition test (How your child thinks and solves problems.)
    - Three tests of cognitive control (The way your child can decide to listen and look, start and stop.), working memory (How your child remembers

and use the things he/she hears and sees.), executive function (How your child plans his actions), planning and organizing of information.

These tests should take about 60 minutes. The entire process will therefore take about 90 minutes.

With your consent you can provide the researcher with two contact numbers, that will be kept confidential. The researcher will then be able to contact you if any further information is required, or information is found to be missing.

If you decide to participate, you will receive a food hamper as a token of appreciation. Your child will be able to choose a toy to say thank you for his/her participation.

If you have any questions, please contact me or my supervisor.

Regards

Annemarie McGovan
maraaiza@gmail.com
081457 6836

Supervisor: Prof Gill Nelson
Gill.Nelson@wits.ac.za
011 717 2138

Appendix E: Informed consent

THE EFFECT OF EXPOSURE TO ENVIRONMENTAL MANGANESE ON NEUROBEHAVIOURAL FUNCTION OF CHILDREN AGED 5 TO 10 IN MEYERTON, SOUTH AFRICA

I _____ (parent /legal guardian) of

_____ (child's name)

acknowledge that:

- I have read the information and understand the content.
- I understand my child's participation is voluntary, and he/she may withdraw at any time without any consequence.
- I understand that confidentiality is important and will always be maintained.
- The results of this study are for academic purposes and do not measure how well your child is taught at school or how he/ she will do academically.

☐ I give consent for my child to participate in this study

☐ I consent to the researcher contacting met if further information is required, or if information is found to be missing.

If yes, please provide 2 contact numbers.

Number 1: _____Number 2: _____

Signed: _____

At: _____

Date: _____/_____/ 20_____

[participant number. _____]

Appendix F: Informed Assent

THE EFFECT OF EXPOSURE TO ENVIRONMENTAL MANGANESE ON NEUROBEHAVIOURAL FUNCTION OF CHILDREN AGED 5 TO 10 IN MEYERTON, SOUTH AFRICA

I _____ (child's name) know and understand

- What the lady explained she will do and why.
- I can stop taking part, any time, if I want to.)
- nobody will know what I answered.

☐ I agree to take part in this study

Signed: _____

At: _____

Date: _____/_____/ 20_____

[participant number. _____]

Appendix G: Letter to Principal

The effect of exposure to environmental Manganese on Neurobehavioural function of children aged 5 to 10 in Meyerton, South Africa

Dear Mrs Radebe

My name is Annemarie McGovan and I am a student at the University of the Witwatersrand. The above-mentioned research project is to fulfill requirements for a master's degree by Dissertation with the Wits School of Public Health.

The proposed study is directed at children who receive schooling close to a manganese smelter and are exposed to airborne manganese. The aim is to evaluate specific identified cognitive behaviors and motor development of the selected children, describe the performance and describe the association of this behaviors with their proposed exposure at school and at home.

This letter serves to inform you of the proposed research to take place at Sicelo Primary School. The school will be used as the recruitment base as well as the site where the initial study and assessments will be completed.

Learners' participation is entirely voluntary, and they will be able to discontinue participation at any stage during the study. There are no direct benefits for participation and there are no identified risks.

All information and results will be treated as confidential, and the learners will not be prejudiced because of participation or non-participation to the study. It is also important to note that none of the results of the study can be used to reflect either positively or negatively on the school or education model.
It would be appreciated if I could be allowed to randomly select 204 learners from the registration register, based on their residential addresses.

Selected learners' parents will be contacted either by telephone or letter to be sent home with the learner. A meeting will be arranged at the school, after school hours at the parent's convenience. The aim and procedure of the study

will be explained in full and the parents will have the opportunity to consider the information and then give informed consent (implying that they received the information, understand it and are willing to have their child participate in the study). The child will also be asked to give assent (implying he/she understands what will be expected of him/her and are willing to participate). The following will be expected of each learner who participates in the study:

1. They will be asked to complete a questionnaire with the investigator (me) regarding background, demographic, developmental and medical information. This will take about 30 minutes.
2. The child will be asked to do the following tests:

- Two motor tests: 1 balance and 1 fine motor and dexterity test.
- A general cognition tests
- Three tests of cognitive control, working memory, executive function, planning and organizing of information.

These tests should take approximately 60 minutes. The entire process will therefore take about 90 minutes.

The assessments are planned to take place from August 2019 to March 2020. The research will in no way affect the learner's academic timetable.

Confidentiality is very important. All data (electronic and material) will be kept in securely locked room and password protected electronic devices.

It is envisaged that the results of this research will be used for academic purposes and a dissertation will be published.

If you are willing to allow me to conduct my research project at your school, please would you complete and sign the attached forms and return them to me as soon as possible.

If you have any queries regarding any aspect of the project, please do not hesitate to contact me or my supervisor.

Regards

Annemarie McGovan
maraaiza@gmail.com
081457 6836

Supervisor Prof: Gill Nelson
Gill.Nelson@wits.ac.za
011 717 2138

Appendix H: Information to School governing body

The effect of exposure to environmental Manganese on Neurobehavioural function of children aged 5 to 10 in Meyerton, South Africa

Dear members of the SGB

My name is Annemarie McGovan, and I am a student at the University of the Witwatersrand. The above-mentioned research project is to fulfill requirements for a master's degree at the Wits School of Public Health. The aim of my research is to evaluate cognitive behaviors and motor development of children, describe their performance, and describe the association of these behaviors with their exposure at school and at home.

This letter serves to inform you of the proposed research to take place at Sicelo Primary School. The school will be used as the recruitment base as well as the site where the assessments will be completed. Learner's participation is of an entirely voluntary nature, and they will be able to discontinue participation at any stage during the study. There are no direct benefits for participants, and no identified or anticipated risks.

All information and results will be treated as confidential, and the learners are at no risk of prejudice because of participation or non-participation to the study. None of the results of the study can or will be used to reflect positively or negatively on the school or education model.

The selected learners' parents will be sent a letter to be taken home by the learner. A meeting will be arranged at the school, after school hours and at the parent's convenience.

The aim and procedure of the study will be explained in full and the parents will have the opportunity to consider the information and ask questions. If they agree to participate, they will be asked to sign an informed consent document.

The child will also be asked to give assent (implying that he/she understands what is expected and is willing to participate).

The following will be expected of each learner who participates in the study:

3. They will be asked to complete a questionnaire with the investigator (me) regarding background, demographic, developmental and medical information. This will take about 30 minutes.
4. The child will be asked to do the following tests:

- Two motor tests: 1 balance and 1 fine motor and dexterity test.
- A general cognition tests
- Three tests of cognitive control, working memory, executive function, planning and organizing of information.

These tests should take approximately 60 minutes. The entire process will therefore take about 90 minutes.

The assessments are planned to take place from August 2019 to March 2020. The research will in no way affect the learner's academic timetable.

Confidentiality is very important. All data (electronic and material) will be kept in a securely locked room on password-protected electronic devices.

The results of this research will be used for academic purposes and a report will be submitted for degree purposes. An academic paper will also be written for publication on a scientific journal. There will be no mention of the school in the paper.

If you are willing to allow me to conduct my research project at Sicelo Primary School, please will you complete and sign the attached forms and return them to me as soon as possible.

If you have any queries regarding any aspect of the project, please do not hesitate to contact me or my supervisor.

Regards

Annemarie Mcgovan
maraaiza@gmail.com
081457 6836

Supervisor Prof: Gill Nelson
Gill.Nelson@wits.ac.za
011 717 2138

Consent and participation in Research project:

The effect of exposure to environmental Manganese on Neurobehavioural function of children aged 5 to 10 in Meyerton, South Africa

Consent sheet SGB (School governing body) of Sicelo Primary School.

Please complete and return this page by _____2019 to indicate if the researcher can continue with the intended study.

I acknowledge that:

- I have read the information and understand the content.
- I understand that learner participation is voluntary, and he/she may withdraw at any time without any consequence.
- I understand that confidentiality is important and will always be maintained.
- The results of this study are for specific academic purposes and cannot be used to indicate or implicate any curricular activities.

I, _____ (chairperson of the SGB)

Name printed

Agree to the above points and allow for A. McGovan to conduct her research at our school

Sicelo Primary School.

Chairperson of the SGB signature:

_____

Date: _____

Appendix I: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Ms A McGovan
School of Public Health
Division of Occupational Health
Medical School
University

E-mail: maraaiza@gmail.com

CC: Supervisor: Professors G Nelson and B Racette <Gill.Nelson@wits.ac.za> and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2020/10/30

REF: *R14/49*

PROTOCOL NO: **M190853** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *The effect of exposure to enviromental manganese on the neurobehavioral function of children in Meyerton, South Africa.*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Ms A McGovan

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M190853

NAME: (Principal Investigator)	Ms A McGovan
DEPARTMENT:	School of Public Health Division of Occupational Health Medical School University
PROJECT TITLE:	The effect of exposure to enviromental manganese on the neurobehavioral function of children in Meyerton, South Africa.
DATE CONSIDERED:	2019/08/30
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professors G Nelson and B Racette
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/10/30

This clearance certificate is valid for 5 years from the 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 on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
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 submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **August** and will therefore reports and re-certification will be due early in the month of **August** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

Appendix J: Photograph consent and release

Photograph release consent.

I hereby give Annemarie McGovan, a MSC student at Wits university, permission to take and use photos of me/ my child.

These photos will only be used for reporting on the progress of the study or reporting the findings of the study.

No findings will be linked to the photo.

Signed _____ Name: _____

Name of child: _____ Child's signature: _____

Date: