An epidemiological cohort study of children and adolescents investigating neurobehavioural effects from pesticide exposure and e-media use in South Africa

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"Writing is a distinct process, not an extension of research or thinking…the time spent on this process- 'rumination time' – is not wasted"

Tim Albert

"…closure can be discovered in the interim as much as it is attained through reaching the end goal…"

Shala Mhlanga

"The whole is different to the sum of its parts"

Kurt Kofka

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Summary

Background

Developmental neurotoxicity is currently referred to as the “silent pandemic” amongst children worldwide. Changes over time in the Global Burden of Disease (GBD) estimates of mental and substance use disorders have contributed to a shift in epidemiology. Although genetic factors play a causal role, environmental and behavioural factors are amongst the highest risk factors regarding disability-adjusted life years (DALYs) in the Global Burden of Disease. Industrial chemicals, air pollution, residential radon, and alcohol use fall within these environmental and behavioural risk factors. The associated neurodevelopmental disorders to these toxicants include Autism, Attention Deficit Hyperactivity Disorder and other cognitive disabilities. Several studies reveal associations to featured symptoms or partial characteristics of these disorders, including behavioural and or learning difficulties. These neurobehavioral difficulties may go unnoticed, yet impact on the cognitive functioning, learning and mental health of children in everyday life. Limited studies investigate risk factors related to chronic exposure at sub-toxic level on these outcomes. This study aims to investigate chronic neurotoxic effects of pesticides on the neurobehavior of children in the Western Cape of South Africa by including potentially relevant co-exposures from the use of electronic-media and maternal alcohol use.

To determine the effects on neurobehavioural difficulties in children living in the Western Cape, South Africa, this study is embedded in the South African-Swiss Bilateral SARChI Chair in Global Environmental Health, an ongoing pesticide exposure project, and the Child Health Agricultural Pesticide Cohort Study in South Africa (CaPSA). This project has a longitudinal design with a cohort of 1,000 school-going children between 9-16 years old. The study was conducted in three different agricultural farmland areas of the Western Cape region of South Africa, from which learners and their guardians were randomly selected from seven schools and categorised into the farm and non-farm residence. The study design conducted over three years included measurements at baseline (2017), follow-up (2019), and repeatedly in between to capture variation. Exposure assessment is measured through participant, guardian and farmer questionnaires on pesticide exposure, co-exposures, and relevant confounders. Objective measures using environmental sampling of air, water, and soil samples as well as biomonitoring of short-term biomarkers in urine, long-term biomarkers in hair, and geographical coordinates were collected over time to validate self-reported data and determine individual exposure variation.

Methods

Cross-sectional analysis using self-reported exposure data with standardised health outcome tools were employed in this thesis to assess the hypothesis testing under study: children who report exposure to the

environmental factors in this study, will have lower neurocognitive functioning and higher health symptoms compared to those who report no exposure.

The primary health outcome on neurocognition was assessed using the software assessment tool, the CANTAB, (with the ability to measure small cognitive changes between groups) and secondary outcome measures included the headache impact screening tool (HIT-6), sleep disturbance questions, and the Health Related Quality of Life tool (HRQol).

We aimed to determine the association between pesticide exposure and neurobehavioural health outcomes by including co-exposures of e-media and maternal alcohol use through the following objectives in each chapter of this thesis:

Chapter 2: The protocol paper which describes the methodology and the prospective cohort study in detail

Chapter 3: The association between e-media use on symptoms and neurocognitive outcomes

Chapter 4: The association between maternal alcohol use exposure on neurocognitive outcomes

Chapter 5: The association between the main environmental exposure to agricultural pesticides on the headache symptom and neurocognitive outcomes

Linear regression analysis was conducted with exposure proxies and health outcome scores as described in each chapter.

Results

Of the 1,001 grade two to nine students assessed at baseline from seven schools, participants are equally distributed across three study areas, equally proportionate in gender, with the youngest age group, 9-11 years more highly represented (60%) than the 12-16 year olds (40%) in the cohort. An almost equal percentage of the cohort report farm (46%) and village (56%) residence. 66% report having a family member including a sibling, parent, grandparent or other who works on a farm. 80% of the cohort report seeing pesticide spraying activities in nearby fields and just over 20% report having ever helped with cleaning farm equipment and assisting with pesticide storage in the past seven days. Of the 32% who report using a mobile phone and other electronic media devices with a smaller percentage connecting with the internet, the majority live in the area closest to the city. Other lifestyle covariates of this cohort include 33% who report a head injury and 15% who report to smoke and drink alcohol. Of the 482 subset guardian surveys collected, 10% of the mothers report gestational drinking, 29% past drinking and 27% report current drinking. Additional socio-demographics describing this sub-set of the cohort include 36% maternal unemployment, 41% maternal education at primary school level or lower, 38% live in a household of 5-6 members, 24% with seven or more members in a household, and 68% are qualified for government child support grants.

Findings

Preliminary patterns of association indicate an overall detrimental health effect on sleep disturbance, headache severity and lower HRQoL from high exposure-related behaviours of mobile phone calls (≥6minutes a day->1 hour/day), night-time mobile phone awakenings (≥1 time/week up to 7 times/week) and mobile phone addiction (36-91 score). Amongst those reporting regular night-time awakenings (≥1 times per week) from mobile phones, HRQol declined by 2.9 (95% CI: −6.1, 0.3), the sleep disturbance score increased by 2.0 (1.1, 2.9) units and headache impact score significantly increased by 5.4 (2.6; 8.2) units compared to the non-exposed group. Mobile phone ownership was a significant predictor of socio-economic status. Contrary to literature, we observe beneficial health effects on neurocognitive performance in all three domains, across all exposure proxies, especially for the moderate-media users, even after stratifying by age and socio-demographic factors. We observe significant predictors of area, alcohol use, head injury, and farm residence in these associations. Non-significant negative associations were found between maternal drinking behaviours and executive functioning. Significant predictors include the child's age, sex, home-language, maternal employment, and household-size on executive functioning.

We identified high-risk exposure groups for pesticide-related activities, eating and picking crops off the nearby field, vineyard or orchard, as well as for storing pesticide equipment, on headache severity and lowered neurocognitive scores in memory and attention. About 50% of the cohort report engaging in behaviors related to pesticide exposure including work activities, eating crops directly from the field and leisure activities of playing, swimming or bathing in nearby water. Headache severity was consistently increased in relation to the three behaviors related to pesticide exposure, work activities (Beta: 1.99 [95% Confidence Interval: 0.86, 3.12]) eating crops (1.52 [0.41, 2,67]) and leisure activities (1.25 [0.18, 2.33). For neurocognitive outcomes, we observed an overall non-significant negative trend with pesticide exposure-related activities. Picking fruits directly from the vineyard or orchard was associated with lower paired associates learning (-0.88 [-1.60; -0.17]) and spatial working memory (-0.29 [-0.56; -0.03]) compared to those who do not pick crops off the field. Smaller differences were associated for eating fruits directly from the vineyard or orchard with lower motor screening -0.06 (-0.11,-0.01) and reaction speed -0.13 (-0.28, 0.10). We observed significant predictors of head injury and alcohol use for lowered neurobehavioural outcomes in these associations and learners who repeated a grade. Socio-demographic predictors include, home-language other than Afrikaans, maternal employment and learners who repeated a grade.

These negative trends are observed across regression models, in line with the hypothesis under study and coherent with literature.

Conclusions and recommendations

This study has gained insight into the environmental and behavioural determinants of pesticide exposure and e-media use on the neurobehavioral functioning of children in the rural LMIC of South Africa. We observe cross sectional associations in support of our hypothesis, warranting further investigation through longitudinal analysis with objective measures. in the next steps of the CapSA study.

Preliminary evidence on associations suggest adverse health effects and that several structures are at play, requiring further understanding of this multi-layer-framework. Lifestyle behavioral aspects related to the exposures, are crucial determinants to include in the steps toward causal analysis on neurobehavior. Our findings uncover that behaviors of e-media use, indicating dependency through longer duration calls, being woken up several times at night in the week due to mobile phone use and additional problematic aspects implicating decisions for social and emotional well-being, mediates the exposure-outcome relation. Since we observe beneficial results on neurocognitive development amongst moderate users, promotion of a healthy balance to e-media use is essential in this cohort, with the screening for high-risk dependency behaviors and associated health symptoms.

Overlapping environmental determinants in a rural LMIC setting with a history of apartheid and perpetuated disadvantage, poverty, and inequality in education and employment, create a highly complex socio-economic setting. This setting presented a suitable diverse context to unpack the complexity due to multiple risk factors. An epidemiological approach to understanding the cause of neurobehavioral difficulties in a rural LMIC, by exploring co-exposures, and through categorised exposure assessment, supports the efforts to unmask the true contextual health effects, and consequent confounding which may hinder comparability to findings from international studies if not adjusted for.

Our findings highlight that behaviors related to environmental pesticide exposures in children and adolescents should be investigated in health impact assessment, to identify high-risk groups who may reinforce the hazardous exposure to pesticides through ongoing dermal contact. While there are several hierarchical factors which contribute to pesticide exposure, from the most distant SES, implicating the disadvantage in education and language of safe use, to perpetuating industry sales of HHPs, behaviour related to the exposure should be considered in future research for comprehensive effective strategies of health intervention.

The CANTAB proved high quality data in its ability to identify chronic exposure health effects in a rural LMIC context and should be promoted in future studies for consistent findings on these topics. Strategies to raising awareness of health symptoms should be implemented in existing school intervention programmes, through parent workshops, and by means of e-media. An empowering approach may upskill this community and the children themselves on digitization and alternate methods of farming for safe use practices. Regular screening of hazardous work and leisure behaviours should be prioritised by all role players including parents, government, and industry. Qualitative research is an additional element for in-depth insight and understanding of this community’s perceptions on health and risks. The lack of infrastructure to carry out effective strategies should be managed with continuous health impact assessment and the investment of industry and government to address the issue at secondary level by testing all chemicals for neurotoxicity, providing guidelines on public health pesticides, removing HHP sales, enforcing restrictions, and regular screening for children at risk of environmental toxicity. Primary prevention should include alternate farming methods, alternate household and agricultural pesticide use and applications, and at a policy level, to enforce stricter regulations regarding the proximity of households and schools to farms in agricultural settings.

Abbreviations

CAPSA	Child Health Agricultural Cohort Study in South Africa
BDD	Behavioral Developmental Disorders
EDC	Endocrine Disrupting Chemicals
HHP	Highly Hazardous Pesticides
HIA	Health Impact Assessment
HRQoL	Health-Related Quality of Life
HIT6	Headache Impact Test-6
LMIC	Low Middle-Income Country
MPPUS-10	Mobile Phone Problematic Use
ND	Neurodevelopment
SES	Socio-economic Status
SDG	Sustainability Development Goals
Swiss TPH	Swiss Tropical Public Health Institute
SARChI	South African Research Chairs Initiative
WHO	World Health Organisation

Chapter 1

1. Introduction

1.1 Neurobehaviour and the burden of non-communicable disease

Neurobehaviour is the performance of cognitive and psychomotor functions. It is at the forefront of neurodevelopment which encompasses the growth and development of the brain through neural pathways. Disruptions of this neural pathway process at various stages of development pose neurobehavioural difficulties in the functioning and performance of everyday activities, including difficulties with cognition, memory, learning, development, social and emotional mental health. A 2010 national health survey estimates that 10-15% of all births are affected by neurobehavioural disorders. [1] The World Health Organisation (p.14) confirms that 15 % of children globally have neurodevelopmental disorders, the most common of which include learning disabilities, developmental delays, Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), reduced intelligence, and cerebral palsy. [2] The 2015 global prevalence rate per thousand for these disorders is: Autism Spectrum Disorder (62 212.2), Attention Deficit Hyperactivity Disorder (51 094.3), Idiopathic developmental intellectual disability (92 074.0), including high prevalence rates of other neurobehavioural difficulties alongside depressive disorders (311 147.6) and anxiety disorders (267 202.4) (p.1568). [3] The Global Burden of Disease estimates of 2015 has described the epidemiological shift as a result that 18 of the 20 leading causes of Years Lived with Disease (YLD) are attributable to non-communicable diseases, including mental and substance use disorders (p.1545). [4] Depressive disorders have shifted from the 4th to the 3rd leading cause, Autism Spectrum Disorder has shifted from the 17th to 16th, anxiety disorders has remained 9th, and other mental and substance disorders have shifted from 19th to 20th on this list (p. 1578). [5]

1.2 Epidemiology and determinants of neurobehaviour in children

Epidemiology, the study of what has come upon people, is a tool for improving public health, which aims to promote, protect and restore health. [6] Epidemiology can be used to describe the health status of a population and determine the cause of disease and its influence on health. The disease is not merely caused by genetic factors but can be an *interplay* of genetic and environmental factors; biological, chemical, psychological, physical, economical or cultural factors, as well as a personal behaviour, can affect health. [6] According to the WHO, factors such as *where we live, the state of our environment, our income and education level, and our relationships with friends and family all have considerable impacts on health*. [7] Several environmental exposures are suspected to affect neurobehaviour. According to Gestalt Field Theory and phenomenology, one's health status is seen as a whole, in relation to the environment. This theory runs parallel with the WHO view on health as an influence of the individual's environment and circumstance as much as it is behavioural. Epidemiology is therefore concerned with the concept of causality and how to untangle these influential effects.

1.2.1 Environmental exposures affecting neurobehaviour in children

In accordance, the World Health Organisation (p.49) summarizes that neurodevelopmental disorders are affected by many genetic and environmental factors; neurodevelopmental disorders carry a major economic and emotional burden on society; exposures to environmental chemicals contributing to the neurodevelopmental disorders are poorly understood; and, lastly, those neurodevelopmental disorders are to a great extent preventable through a coordinated plan to identify and alleviate relevant risk factors. [2] Grandjean and Landrigan (2014) concur that only between 30-40% of neurodevelopmental disorders are caused by genetic factors, the majority is attributable to environmental factors and possibly an interaction between the two. [8]

1.2.2 Multi-causality

Risk factors other than *physiological influences* (genetics, susceptibility to disease) include *social structures* (higher income and social status, employment in good working condition; education levels are linked with poor health, more stress, and lower self-confidence; while greater support from families, friends and communities is linked to better health), *lifestyle influences* (individual behaviours; personal behaviour and coping skills – balanced eating, keeping active, not smoking and drinking, and how one deals with life's stresses and challenges all affect health), and the *physical environment* (safe water, clean air, healthy workplaces, safe houses, communities, and roads which all contribute to good health). [7]. Differences in these settings present different risk factors, causing differences in health outcomes. This, therefore, explains why there are differences in epidemiological observational studies conducted in different settings. To account for this problem, epidemiology views the cause in a hierarchy with varying driving forces, human activities and poor environmental quality operating at distal and proximate causal levels. [6]

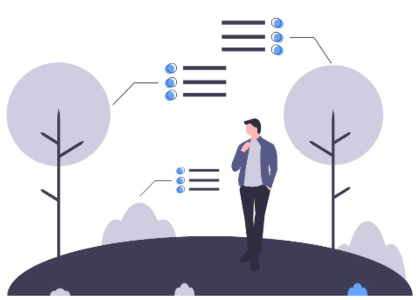

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Image 1 An illustration of the individual in the environment, with varying known and unknown, immediate and distance influences

Furthermore, children are more at risk than adults, due to their different behavioural patterns of contact with the environment, and their still developing organs. The brain is at its peak of development throughout childhood, yet the windows to additional influential risk factors on this development are during early childhood and adolescence. In these later stages, children are less restricted to the home and more vulnerable in cognitive and psychomotor development due to their increased contact with the environment through play, friendship building, and possible involvement with work activities.

In occupational therapy with children, their neurobehavioural difficulties are described as potential sensory overload and intervened at the sensory level of the child to support their nervous system to cope with the environmental stimulants or pressures. Gestalt therapy with a child presenting psychosomatic symptoms and or neurobehavioural difficulties views the pathology as an unresolved cycle of experience in contact with the environment. Sensory awareness is an integral part of the therapeutic process with the child, to bring them into the present and in contact with the unresolved experience, to support them toward closure and supportive techniques for future contact with the stressful situation. Similarly, epidemiology views disease to be caused by contact with a stressor. Epidemiology is concerned with the concept of cause and has a focus on the causal pathway which occurs through contact with the environment through one or more of our senses.

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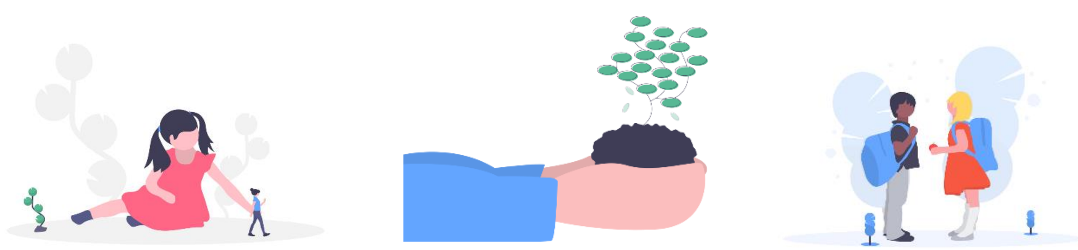

Image 2 Children relate to their environment differently to adults with more contact through their senses

1.3 Exposure assessment in epidemiology and environmental health

1.3.1 Definition of exposure and exposure assessment

Exposure is "contact of somebody with something in an environmental setting". [9] Exposure assessment is *"the process of estimating or measuring the magnitude, frequency, and duration of exposure to an agent, along with the number and characteristics of the population exposed. Ideally, it describes the sources, routes, pathways, and uncertainty in the assessment".* [10] There are three elements and phases of exposure (Figure 1) between the stressor and receptor: the *beginning phase* of <u>emission</u> of an agent into the environment in terms of concentration and intensity; the *second phase* of exposure pathway which refers to the <u>course</u> which the agent takes to reach the subject; the *third phase* refers to the route or mode by which the agent enters the subject; and the last phase refers to the uptake in the subject. [9]

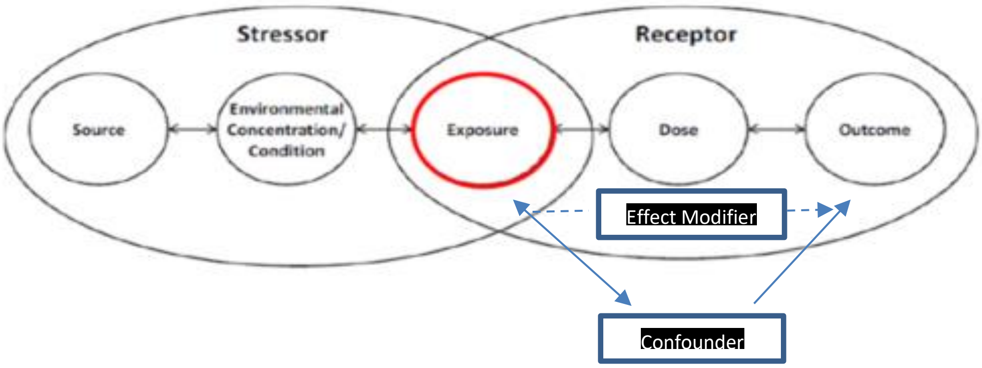

Figure 1 The point of exposure contact between the stressor and receptor (adapted) [9]

1.3.2 Co-exposures in epidemiological studies

Exposure assessment is a method in epidemiology to fulfill the objective of describing an exposure-response with explanatory factors other than those which are primarily studied. [9]

In epidemiology, exposure assessment incorporating co-exposures helps to strengthen the study to understand the association more clearly by identifying the true effect of the main exposure, independent of potential other factors associated with the health outcome under study. If there are other co-exposures in the study population which are determinants of the same health outcome under study, these potential other risk factors may pose problems of confounding (when the effects of two exposure risk factors have not been separated), or effect modifying in the model of association, masking the true effect between exposure and outcome. A Directed Acyclic Graph (DAG) is used in causal analysis to understand these potential other factors which may influence the direct relationship under observation, as illustrated in Figure 1 through the arrows and direction. Confounding, defined by its presence as an independent risk factor to the disease as well as its association with the exposure, may influence the direction of the association or present a cause-effect relationship that does not truly exist.[6] Confounding is seen as one of the main weaknesses of an observational study, without which we cannot conclude association by causality. [11] An effect modifier has the same two relational conditions as the confounder, in addition to its influence on the causal pathway, usually at a biological level. [12]

This study will focus on determining the association, the first steps toward causation, between agricultural pesticide exposures and neurobehavioural outcomes. It will further explore potential confounding or effect modification by including the effects of two co-exposures relevant to neurobehaviour and particularly to this South African rural context: exposure to electronic media (e-media) use and maternal alcohol consumption.

1.4 Physical and lifestyle environmental exposures and neurobehavior

1.4.1 Agricultural pesticide exposure

The use of pesticides in modern agricultural activities has significantly increased in the past century because of an increasing need to secure food sources for growing populations. [13] Since the advent of the green revolution (increased dependence on irrigation, fertilisers and agricultural pesticides) in the 1960s, the gross global food production (cereals, coarse grains, roots and tubers, pulses and oil crops) increased from 1.8 billion tons in 1961 to 4.4 billion tons as of 2007. [14] [15] In 2001, 25% of the 2.26 million tons of active ingredients were used in developing countries where an estimated 25 million cases of pesticide poisoning and up to 20,000 unintentional deaths occur every year. [16] [17] Alongside these acute effects, long-term exposures to pesticides are associated with chronic illnesses including cancer, reproductive and neurological effects. [15] [18] The neurotoxic property of pesticides has been confirmed by experimental laboratory studies, revealing that Europe's current pesticides, including organophosphates, carbamates, pyrethroids, ethylene-bis-dithiocarbamates, and chlorophenoxy herbicides can cause neurodevelopmental toxicity. [19] A few of these pesticides fall within the list of harmful pesticides categorized as Endocrine Disrupting Chemicals (EDCs). Since the ban of highly hazardous pesticides is a long-term process entailing stock piles of obsolete pesticides and phasing out over time at national and regional level in many countries, the Food and Agricultural Organisation recognised the need for pesticide risk reduction associated with HHP use and developed a new initiative in 2007 for a criteria to categorise and label pesticides with toxic properties as HHP: "HHP's means pesticides that are acknowledged to present particularly high levels of acute or chronic hazards to health or environment according to internationally accepted classification systems such as WHO or GHS or their listing in relevant binding international agreements or conventions. In addition, pesticides that appear to cause severe or irreversible harm to health or the environment under conditions of use in a country, may be considered and treated as highly hazardous." [20] In addition, the Code refers to the definition of a hazard: "to mean the inherent property of a substance, agent or situation, having the potential to cause undesirable consequences (eg: properties that can cause adverse effects or damage to health, the environment or property)". [20]

Endocrine-disrupting chemicals (EDCs) are known to alter biological and neurodevelopmental functioning through the ingestion of drinking water, food, inhalation of gases through air or dust, and absorption through the skin (WHO, 2013). These endocrine-disrupting chemicals may be absorbed into the organ tissues over long periods, targeting neurotransmitters Acetylcholinerstrasse (AchE). Different pesticide chemicals properties act on the brain in different ways, but all are at the nerve level – the point of communication between two neurons. The damage is either where one cell is trying to send a signal to the other, or where the other cell is struggling to receive the message that has been sent. Children are more susceptible because their brain development is still ongoing and because they absorb higher levels of the toxicity per body weight than adults, while their behaviours are more vulnerable to the highest route of dermal exposure (Figure 2).

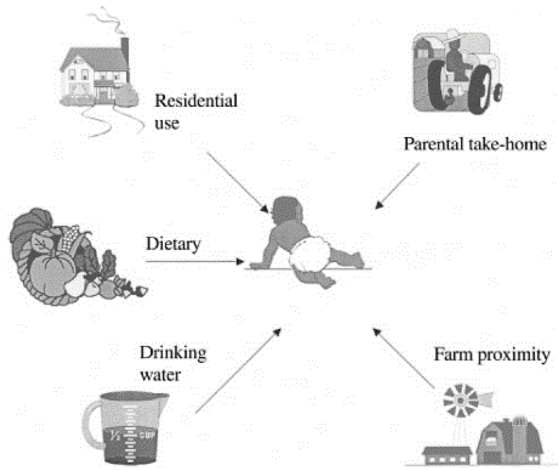

Figure 2 Exposure pathways for children in agricultural communities [21]

Dermal or skin contact is one of the major routes of uptake from the exposure to the stressor, with the following three potential exposure pathways to the child. In Figure 2, specific behaviour related exposures are highlighted on the left, with drinking water, diet, and residential use being three main routes of dermal pesticide exposure in children. The two exposures on the right, parental take-home PPE and the objective farm proximity are additional pathways for dermal exposure. [22]

These harmful effects may occur where requirements for safety testing of pesticides do not include testing for toxicity, especially in developing countries where regulatory and educational bodies are limited, together with the lack of research to inform policymakers. [16 23 24]

1.4.1.1 Acute verse chronic symptoms of neurodevelopmental disorders

Since all children in this study are in a mainstream curriculum school in South Africa, there would be no typically diagnosed neurodevelopmental disorders. If so, the collective features of the disorder would have been identified before the age of nine through the difficulty to cope with learning and as regards behaviour in a classroom setting of 40-50 learners and one teacher. A learner would have repeated a grade and been referred to a specific public school called Learners with Special Education Needs (LSEN) school. The children in this cohort exposed to chronic, long-term, low-level exposures would present subtle effects on the spectrum of a neurodevelopmental disorder, such as specific areas of executive functioning including attention, memory, or processing speed, or more than one of these areas. Chronic exposures present milder symptoms than acute exposures. The WHO International Classification of Functioning (ICF) includes a gradient of how people live with the consequences of the disease, from impairment (mild intellectual difficulty) to disability (difficulty in learning), and, most severely, a handicap where the person may be socially isolated. [6] Children's health symptoms may go unnoticed in these cases of mild impairment, despite the difficulties they may experience with daily tasks and learning. Health symptoms including headache, quality of life and sleep disturbance may be identified endpoints in relation to the neurobehavioural disability health outcome.

Although the literature is very limited in this area of findings concerning chronic environmental exposures on child development, much earlier studies since 1979 began this search to uncover the association between lead and child neurocognitive performance, with the majority of current studies proving inconclusive since only symptoms of the disorder were found. [25] The same problem exists in studies on gestational alcohol exposure – not all children who are affected are identified unless there is the presence of facial features as in the case of the full spectrum of FASD, meaning children on the lower spectrum are thus more difficult to identify. [26]

1.4.1.2 Neurotoxic target areas and assessment of pesticides and co-exposures

EDCs have an effect on learning and behaviour and more specifically on the frontal lobe functions of the brain, the higher cognitive skills including problem-solving, concentration, behaviour, and execution. These functions fall within the three targeted neurotoxic areas of the brain including processing speed, attention, and execution. We want to understand whether the communication between the nerves is affected by long-term neurotoxic exposure by testing their functioning and performance of daily activities, using tasks within specific tests (Figure 5). The World Health Organisation (WHO) has recommended the battery of tests (Figure 3) selected for this study.[27] The Cambridge Automated Neuropsychological Test Battery (CANTAB) has been tested in both human and animal studies and is thus sensitive to detect deficits of executive functioning from environmental neurotoxicity. [28] [29]

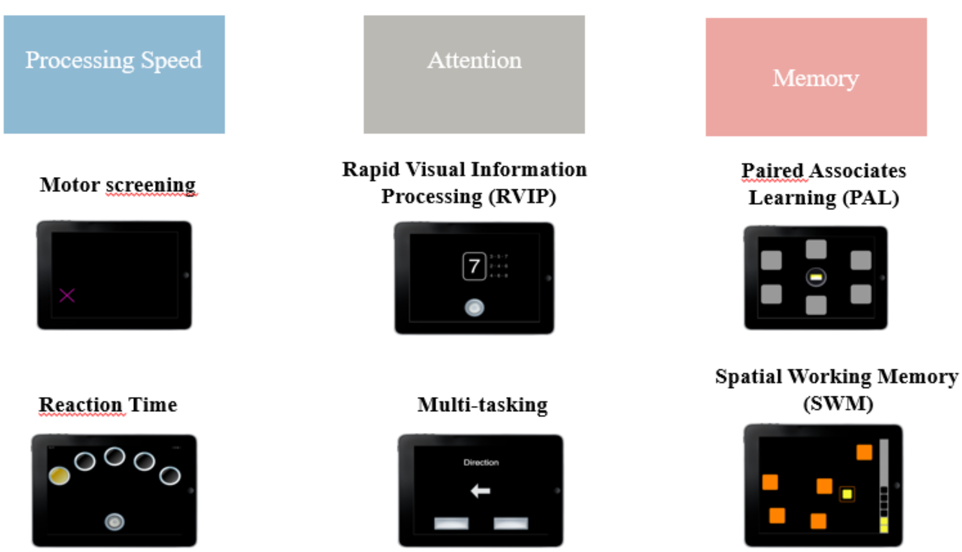

Figure 3: CANTAB Neurocognitive Assessment Tool

1.4.1.3 Neurobehaviour and agricultural pesticide use in South Africa

Statistics South Africa (2010) revealed that the prevalence of children living with these disabilities is 11.2% per 2.1 million children included in the 2009 national household survey. [30] The survey highlights that these disabilities were more prevalent in males than females, and higher amongst the coloured/black population than the Indian/Asian population, naming social, nutritional, and environmental risk factors as a cause for the disparity in population groups.

South Africa, a developing country, is well established in its commercial farming and is one of the largest importers of pesticides, with over 3,000 types of pesticides registered for use including neurotoxic and endocrine-disrupting chemicals such as chlorpyrifos, cypermethrin, and endosulfan. [31 32] Both herbicides and insecticidess are applied in SA in the summer season, including neurotoxic Carbamates, Pyrethroids, and Organophosphates. [33] This corresponds with a study in the rural farmland of the Western Cape, where EDCs where discovered on the surface of drinking water, with levels exceeding the WHO regulations for health and safety. [34] This is further confirmed by the Department of Agriculture, Forestry, and Fisheries (DAFF) of South Africa, which controls the registration of pesticides. Most of these pesticides have not been evaluated for toxicity, meaning their safety has not been reassessed to ensure that they align with the recent stringent standards of risk assessment. [31 32 35] Studies carried out in the local context suggest that the focus of commercial farmers is on economic productivity rather than on health and safety and therefore requires increased monitoring for safer environments, especially since no legislation in South Africa exists to protect its people from these compounds. [36 37]

Of the top 20 pesticides identified as hazardous in South Africa, four are specifically categorized as neurotoxic (Mancozeb, Glyphosphate, Imidacloprid, and Chlorpyrifos). [38]

1.4.2 Electronic media (e-media) use exposure

Another unregulated health and safety risk is associated with mobile phone usage. Research reveals that mobile phones are now as common in South Africa as is in America and that amongst the technological advancement, mobile phone usage is the highest, especially amongst the adolescent age group. South Africa has 149.5 mobile phone use subscribers per 100 people, compared to 91.2 in developing countries, and 71.1 in Sub-Saharan Africa. [39] As a consequence, the exposure to RF-EMF (radiofrequency electromagnetic fields) has increased rapidly in the last few years. This development has raised public concerns regarding adverse mental health effects, especially in young people due to their still developing nervous system. A Swedish study found that the duration of mobile phone and cordless phone calls is associated with self-reported concentration difficulties in adolescents and the number of mobile phone calls was associated with impaired attention performance in

Australian adolescents. [40] [41] Using mobile phones for entertainment was found to be associated with Attention Deficit Hyperactivity Disorder symptoms in 2,422 Korean children and inattention in 7,102 Chinese adolescents. [42] [43] In Swiss adolescents, problematic mobile phone use was associated with behavioural problems. [44] More recently, a Swiss study confirmed that mobile devices account for the highest exposure source to radiation absorption in the adolescent brain, with a cognitive impact on figurative memory located on the right side of the brain. [45] Positive associations between poor school performance and problematic cell phone use were concluded in two studies. [46] [47] However, a more recent study measuring dose-response concludes that these symptoms of ill health were associated with extensive wireless device use, other than mobile phone use. [48] This study will therefore take into account e-media use and not mobile phone use only. In addition, since more findings, including those mentioned above, are associating the health effects of e-media with behavioural patterns, rather than with radiation exposure, this study will focus on behavioural patterns of e-media use exposure and its effect on the neurobehaviour of children. The World Health Organisation is prioritizing excessive internet use under the management of substance abuse, with the recognition of mental health disorders and its association with the addictive behaviour of electronic devices, internet, and gaming on a global scale. [49]

1.4.3 Maternal alcohol consumption during pregnancy

Fetal Alcohol Syndrome Disorder (FASD) is associated with low socio-economic status in communities of both developed and developing countries. [50] South Africa`s Western Cape Province has the highest rate of Fetal Alcohol Syndrome Disorder in the world, reporting 46 cases per 1000 births, and even higher in recent studies. [50] This struggle dates back to colonialism in the history of South Africans, where no labour laws existed during the apartheid regime, and farm labourers were remunerated in alcohol rather than money, referred to as the Dop (Afrikaans translation for a drink) System. [51] This practice continued long enough to create dependency and the Dop legacy as it is referred to, even though the Dop System was declared illegal after apartheid ended in 1990. Results from a 2008-2010 survey in five farming communities in the Western Cape revealed that 83% of farmworkers were current drinkers compared to 65.5% of those who were not farm workers or in a different occupation; among current drinkers who consumed alcohol in the week preceding the interview, farmworkers consumed almost twice the amount of alcohol compared to others (15.2 *vs.* 8.9 drinks, $p = 0.008$); bingeing (five or more drinks per occasion for men; three or more drinks for women) is more prevalent among farmworkers than others (75.0% *vs.* 47.5% respectively, $p < 0.001$) and men were only slightly more likely to be current drinkers than women, 75.1% *vs.* 65.8% ($p = 0.033$), as females reported that they were under more stress than males. [52] Concurrently, London (2000) found that workers in the South Africa deciduous fruit industry with past experience of the Dop System were almost 10 times less likely to be abstainers from alcohol than colleagues without exposure to the Dop System. [53]

1.5 Framework and objectives

1.5.1 Swiss South African Joint Research Project (SSAJRP)

This study design is embedded in an ongoing research partnership, South African-Swiss Research Chair in Global and Environmental Health (SARChI) partnership.

In 1998, Professor Aqiel Dalvie, director of the Environment and Occupation Health Unit at the University of Cape Town, researched pesticide contamination in three agricultural farmland areas of the Western Cape: Hex River, Piketberg and Grabouw. Neurotoxic and endocrine disrupting chemicals were found on the ground surface and in drinking water. Beside chlorpyrifos and deltamethrin, endosulfan was detected the most, exceeding the European Drinking Water Standards of 0.1 µg/L with 3.16 µg/L found in Grabouw and 0.85 µg/L in Hex River. [54] A follow-up cross-sectional study on pesticide exposure and reproductive health amongst boys in these same areas discovered that boys who lived on the farm (higher exposure) compared to non-farm residents (lower exposure), were shorter, weighed less, and had lower serum luteinizing hormone. [55]

Subsequently, a longitudinal project on the same topic of pesticide exposure and reproductive health outcomes was designed under the SARChI's chairholder, Professor Aqiel Dalvie, as the South African principle investigator, and Professor Martin Röösli as the Swiss principal investigator. This prospective cohort study aimed to include approximately 1,000 learners aged 9-15 years, schooling and living in the three study areas, Hex River, Piketberg, and Grabouw. As a fieldworker on the air pollution study within the research chair, I proposed to integrate a second health outcome on neurobehaviour in the pesticide study, in line with my clinical background and pursued to enquire about the environmental impacts on the neurobehaviour and mental health of children.

1.5.2 Child Health Agricultural Cohort Study in South Africa (CapSA)

The cohort study has the designs and purposes as discussed in Chapter 2 of this thesis to determine the causal effect over time. The hypothesis on the environmental exposure is based on the association of proximity: farm resident children are more highly exposed to pesticides than village resident children. We therefore selected an equal number of children from farms and villages to capture this difference.

The key criterion is for the exposure to precede the outcome when determining the association. This is ensured through the longitudinal prospective component of a cohort design, where the outcome is followed-up and ideally eliminates the issue of reverse causality. Additional to the event sequence, the cohort design has the advantage of determining the aetiology and particularly the cause for chronic diseases which may not be as apparent as in the case of infectious diseases. Although costly and over long periods, the advantages of a cohort study provide the ideal design to explore this health outcome among different exposed groups, with consideration of variation in exposure and individual factors. The goal of CapSA is to develop a health impact assessment of the exposure and health outcomes under study.

This thesis focuses on the objectives related to neurobehavioural health outcomes and association with environmental exposures captured through a baseline survey and neurocognitive assessment data within the CaPSA project. This thesis has both a descriptive and analytic component to test the hypothesis under study and explore the relationship between exposure and outcome. This thesis contributes to the first steps in causal analysis within CapSA and toward the HIA by identifying hazardous neurotoxic exposure pathways in this cohort.

1.5.3 Research aim and objectives of this thesis

This study aims to determine the association between pesticide exposure on the neurobehaviour of children in the Western Cape, South Africa by including potential relevant co-exposures from the use of e-media and alcohol consumption during pregnancy.

We hypothesize that children who are exposed to these environmental factors at a moderate or high level will show lower neurocognitive performance and increased health symptoms compared to children who are not exposed.

1.5.3.1 Objectives of this thesis

The main objective of this thesis it to evaluate the association between pesticide exposure and neurobehavioural outcomes in schoolchildren living in agricultural areas of the Western Cape. To explore relevant confounding factors and effect modifiers on this association, two additional analyses were conducted:

- To determine the association between e-media use exposure and neurobehavioural outcomes
- To determine the association between maternal alcohol consumption during pregnancy and neurobehavioural outcome

The following chapter will describe the epidemiology cohort methodology and design in detail, followed by the three chapters on cross-sectional exposure assessment of the baseline data to determine the association patterns, as outlined in the objectives and aims of this thesis.

Chapter 2

2. Methodology

A prospective cohort study of school-going children investigating reproductive and neurobehavioral health effects due to environmental pesticide exposure in the Western Cape, South Africa: study protocol (CapSA-The Child Health Agricultural Pesticide Study in South Africa)

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BMC Public Health

A prospective cohort study of school-going children investigating reproductive and neurobehavioral health effects due to environmental pesticide exposure in the Western Cape, South Africa: study protocol

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Abstract

Background: Research on reproductive health effects on children from low-level, long-term exposure to pesticides currently used in the agricultural industry is limited and those on neurobehavioral effects have produced conflicting evidence. We aim at investigating the association between pesticide exposure on the reproductive health and neurobehavior of children in South Africa, by including potential relevant co-exposures from the use of electronic media and maternal alcohol consumption.

Methods: The design entails a prospective cohort study with a follow-up duration of 2 years starting in 2017, including 1000 school going children between the ages of 9 to 16 years old. Children are enrolled with equal distribution in sex and residence on farms and non-farms in three different agricultural areas (mainly apple, table grapes and wheat farming systems) in the Western Cape, South Africa. The neurobehavior primary health outcome of cognitive functioning was measured through the iPad-based CAmbridge Neuropsychological Test Automated Battery (CANTAB) including domains for attention, memory, and processing speed. The reproductive health outcomes include testicular size in boys and breast size in girls assessed in a physical examination, and blood samples to detect hormone levels and anthropometric measurements. Information on pesticide exposure, co-exposures and relevant confounders are obtained through structured questionnaire interviews with the children and their guardians. Environmental occurrence of pesticides will be determined while using a structured interview with farm owners and review of spraying records and collection of passive water and air samples in all three areas. Pesticide metabolites will be analysed in urine and hair samples collected from the study subjects every 4 months starting at baseline.

Discussion: The inclusion of three different agricultural areas will yield a wide range of pesticide exposure situations. The prospective longitudinal design is a further strength of this study to evaluate the reproductive and neurobehavioural effects of different pesticides on children. This research will inform relevant policies and regulatory bodies to improve the health, safety and learning environments for children and families in agricultural settings.

Keywords: Pesticides, Low exposures, Reproductive health, Neurobehaviour, Co-exposures, School-going children, Rural communities, Endocrine disruption, Air and water

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Background

Chronic health effects resulting from agricultural pesticide exposure, especially at an early stage of development is an important public health concern globally [1, 2]. Neurotoxic effects leading to learning and developmental disabilities as well as male and female reproductive and developmental adverse effects, are of particular concern with respect to exposure to pesticides for example in the chemical group of the organophosphates, carbamates and pyrethroids [3–6]. Several of these pesticides are hormonally active and listed as Endocrine Disrupting Chemicals (EDC's), which alter biological and developmental functioning at low levels [6, 7]. These harmful pesticides may be absorbed into the organ tissues via ingestion of drinking water, food, inhalation of spray drift or dust and via absorption through skin [7–9].

South Africa, an upper middle-income country has the highest application rates of pesticides in Sub-Saharan Africa with over 3000 different types of pesticide product formulations registered, including the possible neurotoxic and EDC's active ingredients bifenthrin, chlorpyrifos, cypermethrin and mancozeb [10, 11]. The Western Cape is an important crop farming sector in South Africa. Most of the pesticides including herbi- cides and insecticides are applied during the summer season [4]. Amongst the number of pesticides detected in the Western Cape area's surface and ground water that includes drinking water, are chlorpyrifos, delterme- thrin, and endosulfan. Endosulfan was most often detected with levels exceeding the World Health Organisation (WHO) standards of 0.1 μ/L for health and safety [12, 13]. High levels of endosulfan metabolites have also been detected in farm workers and residents of the rural Western Cape [13–15].

A cross-sectional study in the rural Western Cape on the reproductive health and development of school boys found different levels of reproductive hormones, lower sexual maturity ratings and anthropometric measurements, in boys who lived on farms compared to those who did not [16]. A case-control study in the Eastern Cape of South Africa found significant associations of birth abnormalities in the offspring of women exposed to agricultural chemicals during pregnancy, including various organophosphates, blue death (a mixture of carbaryl, carbufuran and campechlor/ toxaphene- banned in South Africa since 1970) and other insecticides [17]. Other than the case control study and the cross-sectional studies aforementioned there are no other studies amongst children in South Africa assessing the causal link between pesticide use and health outcomes. Data is especially limited on longitudinal studies amongst low to aver- age exposure to pesticides and its effects on these health outcomes.

To understand the health effects of pesticides requires a better understanding of other factors affecting the physical and neurobehavioral development. Various studies observed associations between electronic media (e-media) use and behavioral patterns including inattention and wellbeing, mostly attributed to use of mobile phones than to radiation exposure [18–21]. Mobile phones are now as common in South Africa as is in America, and mobile phone usage in daily life is common, especially among adolescents. South Africa has 150 mobile phone use subscribers per 100 people, compared to 91 in developing countries, and 71 in Sub-Saharan Africa [22].

Furthermore, South Africa's Western Cape Province, has the highest rate of Fetal Alcohol Syndrome Disorder (FASD) in the world, with rates higher than 46 cases per 1000 births in recent studies [23]. Previous studies have shown that 46 to 51% of rural woman drink during pregnancy [23]. There are several challenges associated to these high rates particularly relevant in the context of the study areas in the Western Cape: the drinking situation was declared a public health challenge as the fight against alcohol abuse dates back to colonialism in the history of South Africans; no labor laws existed during the apartheid regime, and wages for farm laborers was remunerated in alcohol rather than money, referred to as the Dop (Afrikaans translation for drink) System [24]; FASD is associated 45 times higher amongst woman with lower socio-economic status (SES) than those in middle and upper SES [23]; and the agricultural sector in South Africa is the largest single employment sector, especially for women [25].

The primary aim of this prospective cohort study is to determine the association of agricultural pesticide exposure with reproductive development and neurobehavior of children in the rural Western Cape, South Africa, independent of co-exposures from use of e-media and maternal alcohol consumption. The secondary aim is to investigate associations of these co-exposures on reproductive, neurobehavioral development and well-being of children.

Methods/design

Study design

This research study has a longitudinal design comprising a baseline and a follow-up examination of a cohort of 1000 school-going boys and girls from the rural Western Cape of South Africa. The study design is illustrated in Fig. 1 and data collection tools described in detail under the "data collection tools" section below. Study participants are examined at baseline in 2017 and at follow-up in 2019 using the same exposure survey and pesticide biomonitoring exposure measures, as well as the same health outcome measure tools including the CANTAB.

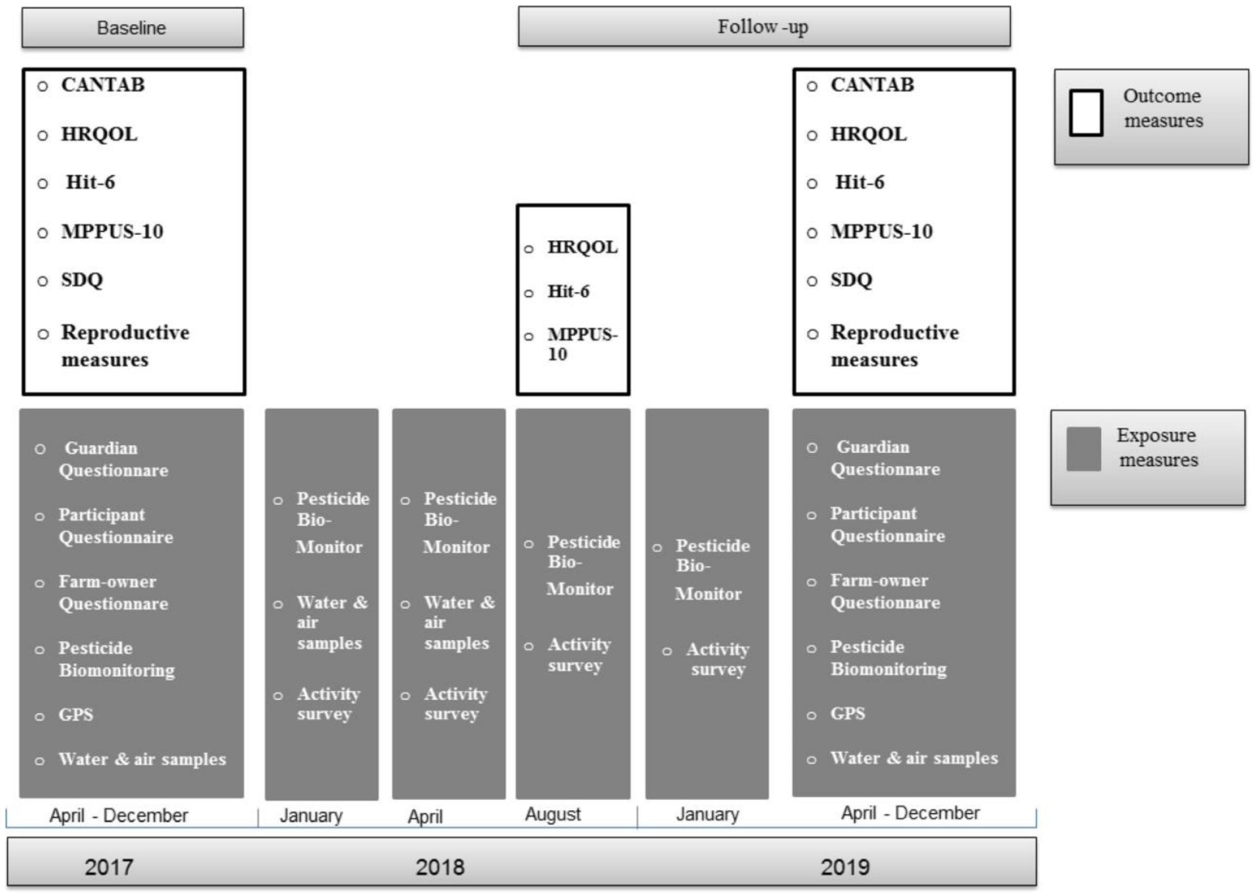

Fig. 1 Illustration of the data collection exposure, health outcome tools and timeline in the cohort study

reproductive measures including i) Tanner staging - a physical examination of the male and female reproductive system (measuring sexual maturity) ii) reproductive hormone levels and iii) anthopometric measurements, Health Related Quality of Life (HRQOL, also referred to as KIDSCREEN), Headache Impact Test (HIT-6) and Problematic Mobile Phone use (MPPUS-10).

This data collection will take place in a suitable setting during school visits. The participants parent or gaurdian are also visited, to conduct an exposure survey with one health outcome tool about their child, the Strengths and Difficulties Questionnaire (SDQ). Additionally, water and air samples will be collected for 1 year (July 2017– June 2018) and Global Positioning System (GPS) coordi- nates will be taken both at baseline and at follow-up. The farmers of the surrounding farms to the schools and those farms on which the children live, are con- tacted to conduct a farm survey on pesticide usage (November 2017–June 2019).

There will be four-monthly follow-ups in 2018 of pesticide exposure measures including biomonitoring (urine samples), and an exposure acitivity survey for the participants only. There will be one follow-up during 2018 for participants on three health outcome tools, the KIDSCREEN, HIT-6 and MPPUS-10.

Study area

The study is conducted in three agricultural areas: the Hex River Valley (table grapes), Grabouw (apple and stone fruits) and Piketberg (wheat and fruit) Fig. 2. The three study areas were selected according to: (i) its intensive agricultural activities applying large amount of pesticides;

1. pesticides previously detected in the environment; and
2. high levels of pesticide metabolites measured in workers and residents from these areas [12].

Sampling

We recruited 1000 children aged 9 to 16 years from schools in the three study areas. The children were enrolled with equal distribution per area, per gender, as well as an equal number of those living on farms and not living on farms. Of the 32 existing schools in all three study areas, only primary, intermediate and combined schools were contacted to prevent loss to follow-up (i.e., children from high schools would have left school before the follow-up examination in 2019).

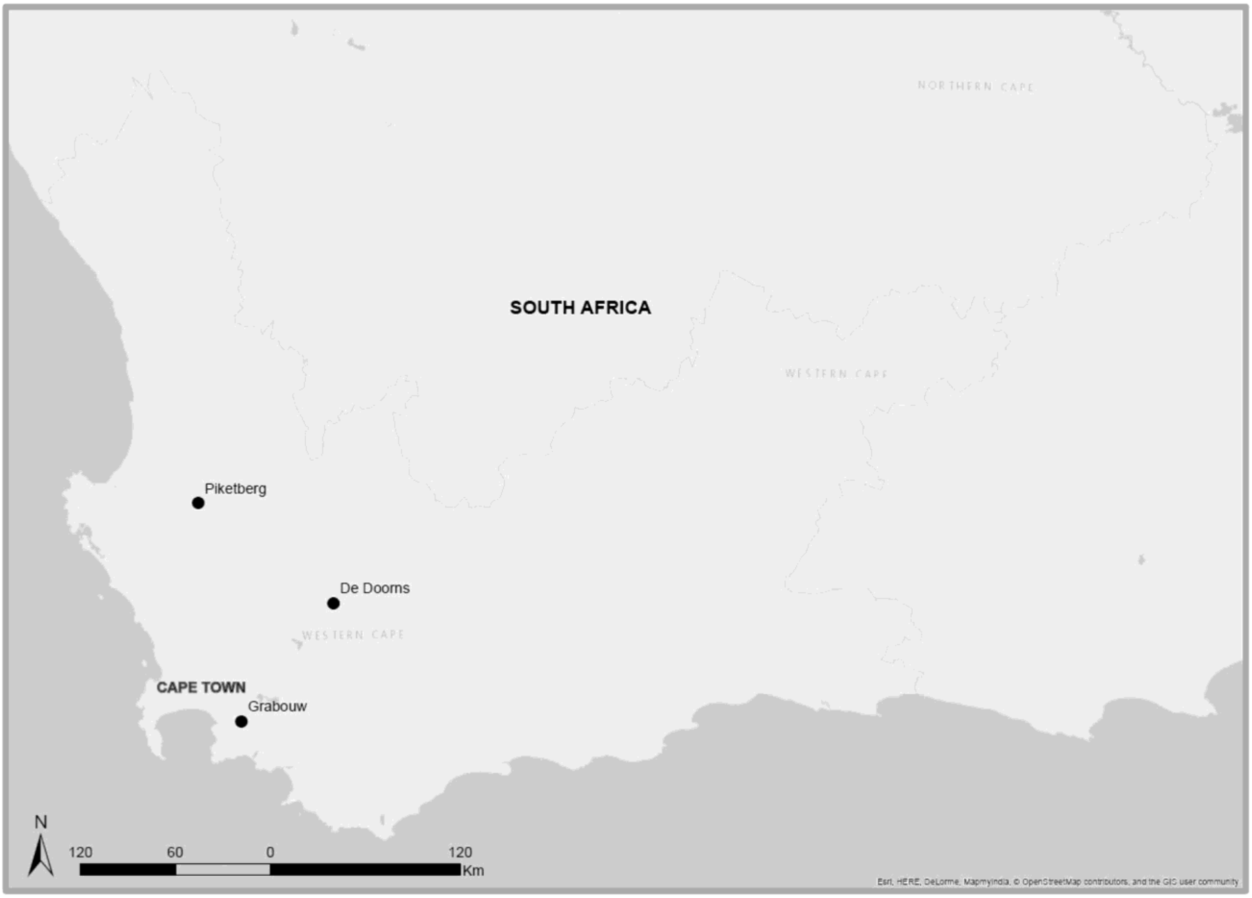

Fig. 2 Map of the three study areas, Piketberg, DeDoorns and Grabouw, in the WC of SAMap made by SM using ArcMap 10.5, © OpenStreet Map

Of the 22 intermediate schools, 12 were willing to participate and four of the seven combined schools were willing to participate.

The principals and governing bodies of these 16 schools were contacted and informed about the study and seven agreed to participate. In these seven schools, information sheets about the study and the role of the school in this study together with permission letters was then sent to the parents or guardians of all the school children in grades four to nine via their children. The letter served as an invite to participate in the study which had to be indicated by signing and providing detailed contact information. In schools where the number of consenting parents or guardians exceeded the number of children targeted, random systematic sampling was to be used to select the children. Consent from parents or guardians who responded to the study invitation were obtained through home visits.

The grades were expanded from only including 4, 5 and 6 to include grades 2, 3, 7, 8 and 9. Learners from these selected schools were found in these lower and higher grades while still fitting the age criteria, 9–16 years, for the study.

Data collection tools

Neurobehavioral health outcomes measurements

Cognitive assessment

The online CANTAB Connect Research, developed by Cambridge Cognition, comprise several domains of cognitive testing [26]. The CANTAB is specifically sensitive to changes in neuropscyhological performance and has been applied in over 1750 peer reviewed publications of both human and animal studies [27–29]. Cognitive domains including processing speed, attention, and memory were selected for testing in relation to targeted areas of pesticide and alcohol neurotoxicty. Two tests per domain are selected to measure specific cognitive functions within each of the three domains as shown in Table 1 [30–32]. The CANTAB has different levels for each test to accommodate age variation. The lower levels in each test were selected for this studies age range. Each test is presented to study participants through an iPad (Apple Air, 9.7”) with the installed CANTAB software during the school visit. The time to complete the whole battery requires 40 min from each participant. Each CANTAB test measures cognitive functionining by recording

Table 1 Cognitive domains and tests performed within the CANTAB cognitive assessment battery

	Cognitive domain	Test	Cognitive function	Outcome	Duration
1	Processing speed including visual motor integration	Reaction Time (RTI)	Perception of visual stimuli, response to visual stimuli and	movement time, reaction time and response accuracy;	6 min
		Motor Screening (MOT)	Sensorimotor or perceptual motor speed and	Time lapse between display to response; number of correct and	2 min
2	Memory including executive Functioning	Spatial Working Memory (SWM)-	Manipulation of visuo-spatial information, executive demands of strategy (reasoning, decision making and behaviour), parts of short-term memory	Visits, re-visits and searches for boxes	5 min
		Paired Associate Learning (PAL)	Visual memory and new learning, episodic memory (collection of past, personal experience that occurred	Incorrect selection, adjustment, problem solving and memory of selection	8 min
3	Attention	Attention Switching Task (AST)	Attentional set-shifting, cognitive flexibility and	Congruency and latency during change	8 min
		Rapid Visual Information Processing (RVP)	Sustained attention and continuous performance, impulse control or	Sensitivity to target and correct responses	7 min

several outcome performance scores on each task including latency and accuracy.

Health related quality of life (HRQOL)
The comprehensive KIDSCREEN tool that measures HRQOL and wellbeing in the areas of physical, psychological, relational support and school enviroment is administered to the study participants [33]. This tool has three different versions and for the purpose of this study's time constraints, the brief general ten question tool using a five point likert scale for response, requires five minutes to complete.

Problematic mobile phone use (MPPUS-10)
The MPPUS-10 is a tool to measure problematic aspects of mobile phone use related to addiction ('withdrawel', 'loss of control', 'negative life consequences' and 'craving') and related to social components (peer dependence) [34]. A recent study on cell-phone exposure in adolescents observed associations of MPPUS-10 with impaired psychological well-being, impaired parent and school relationships and more behavioural problems [18]. Study participants need about 5 minutes to fill in the ten items.

Headache impact test (Hit-6)
Headaches have been reported to be associated with cell-phone usage [35–37]. To address this question the HIT-6, a brief and validated tool to assess for the severity of headaches, will be applied. This six question tool, uses a five point likert scale which will take 5 minutes to complete.

Strengths and difficulties questionnaire (SDQ)
A brief version of the SDQ is administered to the guardian of the child to screen for any behavioral and affective problems in the child [38]. This widely used tool consists of five scales assessing emotional symptoms, conduct problems, hyperactivity, peer problems and prosocial behaviour on five items each answered on a three point Likert scale.

Reproductive health outcome measurements
Blood reproductive hormones
During the baseline and follow-up examinations, a qualified nurse will collect early morning (before 9 am) whole blood samples (5 ml) from 500 male participants. A sample size of 500 boys (based on findings from previous cross-sectional study [16]) is sufficient to assess differences between farm and non-farm boys. Girl participants were not sampled because of limited funding and the reality that they were less likely to undergo phlebotomy than boys. All the blood samples collected from the study site were transported to the National Health Laboratory Services (NHLS) laboratory based at the Groote Schuur Hospital in Cape Town within 24 h for analysis. Blood samples will be analysed for baseline follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, estradiol (E2) and sex-hormone

binding globulin (SHBG). Baseline hormones will be compared to age-related laboratory norm using the same assays. LH, FSH, E2 and testosterone are markers of reproductive function in boys as they are part of the Hypothalamic Pituitary Gonadal Axis and their secretion can be altered by hormonally active pesticides [5]. Significant alterations in the levels of these hormones may signal possibilities of estrogenic, anti-androgenic or other in vivo endocrine disrupting effect [6]. SHBG is measured to correct for testosterone. The NHLS laboratory does not currently have the capacity to measure inhibin, the other important male reproductive hormone that suppresses FSH for homeostatic control.

Physical examination (reproductive assessment and anthropometry)

Trained and qualified male and female nurses will physically examine the boys and girls respectively in a private room at baseline and follow-up and record the information onto a structured data collection form. Height, weight, secondary sexual characteristics and sexual maturity rating (SMR) will also be recorded [39]. The SMR will be derived by assessing penis development (testicular volume) in boys and breast development (breast size) in girls (129). Testicular volume in boys will be assessed using a standardised set of wooden testicular beads called an orchidometer [40].

Genital anatomical abnormalities including the presence of congenital hydrocoeles, undescended testes, congenital inguinal hernias and hypospadias, and the presence of infection and previous injury will also be assessed for in boys. Additionally, testicular consistency will be recorded for boys. For girls, age at menarche, length and frequency of mensuration and breast development or anatomical abnormalities will also be recorded.

Height and weight will be recorded according to standardised methods and using calibrated instruments.

Assessment of self-reported exposures and other relevant information

Participant questionnaires

The questionnaire administered to participant learners at baseline and follow-up include the following exposure sections:

a. Pesticide Exposure: currently living on a farm or not, recent pesticide contact include seeing and smelling pesticides, swimming in nearby dams or rivers and eating crops from the vine
b. Farming Activities: involvement with farming activities like picking fruit, spraying, cleaning or burning containers

Confounding variables to the health outcomes in this participant questionnaire include:

c. Injury and Other Lifestyle Activities: head injuries, sleeping difficulties and substance use.
d. Electronic Media Use: GERoNiMO: Generalised EMF Research using Novel MethOds (including cellphones). To ascertain exposure amongst adolescents in these communities, the European Union project questionnaire, GERONIMO will be administered to enquire about whether they do use electronic media, the type of media usage, activities that they engage with on electronic media devices and the specific time spent engaged with these activities. This tool will be administered before using the MPPUS-10 described under outcome measurements and only those who indicate that they use a mobile phone will complete the MPPUS-10.

The brief pesticide exposure activity questionnaire administered to participants during the four monthly follow-ups include sections (i) and (ii) from the participant questionnaire.

Guardian questionnaires

The questionnaire administered to parent or guardian includes the following exposure sections:

- Pesticide and Household Exposure: previous and current work and residential location, history and current exposure to pesticides during pregnancy, household chemical exposure and childhood pesticide poisoning
- Child Residential History: pesticide exposure in both their current and previous residence

Confounding variables to the health outcomes in this participant questionnaire include:

- Childhood Development: including birth complications and developmental milestones of the child
- Medical History: including hospitalisation, diagnoses and medication
- Child's Diet and Nutrition
- Maternal Smoking and Alcohol Consumption

Farm-owner questionnaire

The farm-owner questionnaire aims to characterise farm activities in three study areas (apple, table grapes and wheat production systems). Therefore, a sub-sample of 20 farms will be selected in each area from the list of farms where children participating in the cohort study are living. Farm owners will be contacted via phone and a meeting will be arranged. If they are willing to participate they will be required to sign an informant consent form to agree to be part of the study to ensure confidentiality of personal data. The data on pesticide use per crop will then be used to develop spatio-temporal crop-exposure matrices (CEMs). The model will provide information on the exposure to individual agricultural pesticides according to the distance to agricultural fields and the season of the year [41].

Pesticide biomonitoring

Spot sampling of urine will be conducted per study participant by professional nurses at each sampling time point. There are five sampling time points which are, the baseline in the first year, three times in the second year and during follow-up in the third year of this project to determine short-term pesticide exposure. Approximately 8 ml if urine will be collected from each participant. Each participant's urine sample will be separated immediately after collection at the collection point into four 2 ml cryovials with color coded caps and stored on dry ice in a cooler box for delivery to the Hair and Skin Laboratory located at Groote Schuur Hospital, University of Cape Town. A cold chain of 2 to 8 °C will be maintained from the moment of urine seperation into cryovials at collection point within 24 h until storage at − 20 °C at the laboratory until they are analysed.

A hair sample, at least 200 mg of hair, will be collected from each participant at each time point in the study, time points stated above, for determining long-term exposure to pesticides. The hair sample will be stored in a aluminium foil at room temperature until they are analysed. This sample will also be analysed by the Hair and Skin laboratory at the University of Cape Town.

The Hair and Skin laboratory will extract and analyse parent pesticides and their metabolites in the urine and hair samples. Currently analysis will be done on commonly used pesticides in the study areas. The initial pesticide analyses will focus on organophosphate metabolites, dialkyl phosphates (DAPs) and pyrethroids (screen) followed by other commonly used pesticides and more specific analyses for individual active ingredients.

In-house validated methods for extraction and analysis of DAPs in urine and hair will be used for each participant. Briefly, DAPs extraction and analysis in urine involves thawing urine samples, one color coded 2 ml vial for each participant in a water bath. A 1 ml volume of the urine sample will be aliquoted into a glass test tube and mixed with a DAP internal standard mixture. The mixture is freeze dried overnight, resuspended in acetonitrile and mixed by vortexing and sonication. The mixture is centrifuged for 10 min at 4000 g and the the

supernantant transfered into a glass test tube and dried with a vacuum concentrator. The dried mixture is reconstituted in 200 µl of mobile phase and 10 µl analysed using liquid chromatography-tandem mass spectrometry (LCMS/MS).

DAPs extraction and analysis in hair involved weighing 100 mg of hair into a Omni tube, washing the hair wit 1 ml water followed by pulversing the hair in 1 ml of water using an Omni BeadRuptor. The pulverised mixture is centrifuged and the supernatant is collected, filtered and subjected to LCMS/MS analysis. Methods for analysis of other pesticides and their metaboolites are currently being developed.

Assessment of yearly variation of pesticides in air and water

We will assess spatial and seasonal variations of pesticide levels in the atmosphere (over six two-month sampling rounds) and in the aquatic environment (12 one-month sampling rounds) from July 2017 to June 2018. Passive air sampling will be conducted using a total of 36 polyurethane foam disks (PUF-PAS) to sample current used pesticides and 12 PUF-PAS to sample organochlorine pesticides. Samplers will be deployed at two locations in each of the three study areas (one within 50 m to agricultural fields and one > 100 m away in a more urban village environment). Of note, PUF-PAS to measure organochlorine pesticides are only deployed at the location within 50 m to agricultural fields [42]. Given that there are uncertainties regarding the efficiency of sorption to PUFs of polar compounds such as pesticides, three XAD-PAS discs will be additionally deployed at sampling location within 50 m to the farm for 6 months to validate the PUF-PAS sampling systems [42].

Immediately after collection, the PUF-PAS or XAD-PAS samples will be put into a cool box (max 8 °C) and transported to the Chemical Engineering Laboratory at UCT where they will be stored at − 20 °C. In addition, one blank will be distributed in each round for both current used pesticides and organochlorine pesticides. PUF disk samples including field blanks will be transported to the Research Centre for Toxic Compounds in the Environment (RECETOX) in the Czech Republic for analyses. We will target 30+ currently used pesticides (registered and banned in South Africa) in addition to selected organochlorine pesticides which are banned for use in agriculture but may persist in the environment.

Passive water sampling will be conducted at one point downstream of the farming area within the Krom River, Hex River and Berg River located in Grabouw, the Hex

River Valley, and Piketberg, respectively. Styrenedivinylbenzene (SDB) disks will be used which allows for con-

tinuous time-averaged water sampling at a monthly interval (sampling will be for 2 weeks each month) [43].

After 2 weeks, the SDB disks will be collected and transported to the Chemical Engineering Laboratory at UCT where they will be stored at − 20 °C. In addition, one duplicate will be distributed in each round for quality control. SDB disk samples including laboratory blanks will be eventually transported to the Swiss Federal Institute of Aquatic Science and Technology (EAWAG) in Switzerland. We will target current used pesticides.

To assess water quality, we will measure water temperature, water level, conductivity and pH when samples are deployed and collected every second week. In addition, monitoring data of daily precipitation and water flow for the three river catchment areas will be accessed from the Department of Water and Sanitation of the Republic of South Africa (DWA).

Geographical location (GPS)

GPS coordinates of the participating children's homes will be collected during the home visits when conduct- ing the guardian questionnaire during the baseline study. This data will be used to calculate proximity to agricultural activities (agricultural land use data are obtained via the Cape Farm Mapper which is a product of the Western Cape Department of Agriculture) which will form part of a pesticide exposure index for each participant. The GPS based proximity index will be more accurate than the one used in a previous study which was based on self reported and tape measurement information [44]. The proximity index, spraying intesity index as determined from spraying records, levels of pesticides in the environmental samples and pesticide bio-monitoring will be used to calculate a pesticide environmetal exposure index for each participant.

Procedure

All personal interviews using a structured questionnaire were installed on mobile devices using Open Data Kit (ODK) application. The GPS coordinates will also be recorded using the ODK application on the mobile phone. To ensure quality of data collection, standard operating procedures (SOPs) are developed and all field workers are trained over a week prior to data collection which will continue at different points throughout the project. The researchers were trained on the CANTAB by the Cambridge Cognition Company product specialists. Two fieldworkers were hired to conduct the CANTAB with specific criteria for the role and were trained on the CANTAB by the research team. The researcher offered continued support to the fieldworkers during the CANTAB data collection, alongside the guidance of the product specialists. Fieldworkers were hired to conduct the interviews with participants, guardians and farm workers and were trained through workshops and role plays on how to conduct the interview using the ODK softwarewith mobile phones and how to record the GPS coordi- nates. The study nurses to perform the physical examin- ation were trained by an Adolescent/Child health specialist who demonstrated how to perform the anthropometric measurements, use of the orchidometer and assessment of sexual maturation using visual material. The nurses were further trained by the study co-coordinators on their role and tasks within the study as well as on the content of the tools to administer. After sufficient training for the field- workers on both the tools and the study itself, two pilot studies were conducted. The first pilot study to test the content and flow of the questionnaires were with 10 partic- ipants (five boys and five girls). The second pilot study was conducted on the first 100 participants to test all measure- ments and its work flow.

Arrangements are made with each school administration for the best logistics including days, time and place to conduct the study. The work flow on days of testing entails five separate data collection stations within appropriate private and quiet venues in each school. At the first data collection station the participants are informed for the second time about the study and given enough detail on the procedure of data collection. Written assent is required at this station. At the second station, learners are examined by a male/female nurse and have their anthropometric measurements taken. After the examination a spot urine sample is collected from boys and processed for transportation to the testing laborator- ies. Thereafter, they proceed to the third data collection station where learners complete the CANTAB assess- ment. The fourth station requires completion of the survey with a fieldworker. The fifth station entails a hair and blood sample by a nurse with the final station creat- ing a space for the learner to debrief if needed and receive a treat for their contribution. All exposure and outcome measurements will require an hour and half from each participant and the study aims to reach 25 participants in 1 day.

Following the first phase of data collection from learners at the school, the second phase includes home visits by the fieldworkers. Here the parent/gaurdian will be interviewed which requires an hour to complete the questionaire. At this occasion the fieldworkers take the GPS coordinates of the study participant's homes and nearest spraying areas. The three follow-up urine samples between baseline and follow-up and the exposure activity questionnaires will then be administered.

The farm-owner questionnaire is administered three times during the study. The first interview was conducted in November 2017 to characterize the farms according to their production system in place and ask participants to provide a copy of their spraying records for 2016/2017 and a copy of their spraying calendars for 2017/2018. Subsequently, the farms are visited and asked to provide a copy of the spraying records in June 2018 and June 2019.

The air and water sampling are conducted during the first phase of the baseline study between July 2017 and June 2018.

Data analysis

Sample size calculations

Neurobehavioural outcomes The sample size for neurobehavioral health outcomes is determined assuming a 0.2 standard deviation from the median neurobehaviour score in the exposed group compared to the control group. This corresponds to observed differences found in studies investigating environmental exposure on neurobehavioral outcomes, using metabolites as the method to assess for pesticide exposure in the Western Cape of South Africa [45–47] in the United States [48] and in Costa Rica [49, 50]. A sample size of 900 was judged to be adequate with a power of 80% and a 5% level of significance.

Reproductive hormone outcomes Sample size calculations for reproductive outcomes were determined using findings from a previous cross-sectional study conducted in the same study areas [16] that showed differences in the same reproductive outcomes as in this study between farm and non-farm residing boys. A two sample-test of equality of means is used (exposed: con- trol ratio = 2:1, i.e. to ensure that more participants are recruited from pesticide exposed areas, power = 80%, confidence level = 95%). The reproductive outcome requiring the highest sample size to show a significant difference in farm versus non-farm boys is for serum testosterone (one of the five hormones to be measured) for which a sample of 498 (i.e. 332 exposed and 166 unexposed) participants are required to ensures sufficient power for the boys in the study. The sample size calculations for boys were considered applicable for girls as all the clinical outcomes were similar and therefore a sample size of 500 girls was targeted to ensure adequate power to test associations between exposures and outcomes.

Data monitoring

The data monitoring is independent of sponsors. The field coordinator and fieldworkers upload the surveys to the server, while the PhD and post-doctoral students together with the principal investigators monitor the data when uploaded.

Statistical analysis

Associations between pesticide exposure levels and the obtained health outcome will be conducted by considering relevant confounders. Outcomes of interest include reproduction and pubertal growth (levels of reproductive hormones; sexual maturity rating, height, weight, BMI). The neurobehavioural primary endpoint is cognitive functioning with two secondary endpoints, psychosocial and emotive functioning, health and well-being. Pesti- cide exposures of interest include bio-monitoring mea- surements, and the pesticide exposure indices derived from pesticide related risk factors including proximity to the field, contact with the field, involvement in farming activities and contact with the parent or guardian. Co-exposures of interest include e-media use including owning a smart phone and or electronic media device/s, internet use and specific involvement in internet activities such as online games. Another co-exposure of interest includes alcohol consumption during pregnancy characterised by maternal prenatal, perinatal and postna- tal alcohol use. Relevant confounders of interest include medical history and current health status, diet, develop- mental history and indoor chemical use/pollution.

Pesticide exposure will be characterised and compared according to following five different levels: (i) self-reported exposure obtained with the participant questionnaire (e.g., reported behavioral exposure profiles); (ii) self-reported exposure obtained with the guardian questionnaire (e.g., farm worker versus non-farm workers; living on a farm; GPS coordinates of the household and proximity to agricultural fields); (iii) concentration of metabolites and active ingredients measured in urine and hair samples of children; (vi) collected spraying plans and records from farm-owner interviews (to establish pesticide emission profiles for apple, table grapes, wheat and citrus farms and develop a Crop Exposure Matrix (CEM); and (v) measured concentration of active ingredients in passive air and water samples.

Firstly, cross-sectional analyses at baseline and final-follow-up will be conducted. Methods including multiple imputations will be used to address any missing data in the analysis. Further, various types of longitudinal analyses will be conducted. Change analyses will consider whether changes in exposures are related in changes in outcomes. A cohort approach is applied to explore whether exposure at baseline results in new incident cases and provides us the opportunity to assess developmental processes during the time of follow-up. Either clinical case definition is used or in the absence of the criteria for a specific outcome, a priori defined cut-off is used such as the 75th percentile.

Depending on the outcome, logistic, linear or ordinal regression modeling will be conducted.

To maximize power outcomes and exposure, a re-

Linear and logistic regression modeling will be used. Exposure variables may be dichotomised or cate- gorised for easier communication if suitable.

Study population

In total, 1400 invite letters were returned from the parents who showed interest to participate. 1001 study par- ticipants and their guardian/parents from this pool consented and took part in the baseline examination between April and September 2017. Table 2 gives an overview about the study population and basic demo- graphic information.

Table 2 provides descriptive data on the participants in this study, showing they are close to equally distributed amongst the three study areas. The participants age ranges from 9 to 16 years with the highest numbers, almost 60% falling in the younger category of 9-11 years. Their gender is almost equally distributed, with 5% more females than males. The grades range from 2nd to 9th grade, with 66% of the participants falling within the middle category, 4th–6th grade. 46% of the participants live on a farm and 66% have a family member who is a farm worker. Further regarding pesticide exposure, 80% of the participants have said yes to having ever seen pesticide spraying activities in the nearby field; 23% have responded to having helped with cleaning farm equipment in the past; and 20% of the participants have assisted with pesticide storage in the past 7 days. In terms of the participants engagement with electronic media use, specifically mobile phones, 31% use a phone and of those who use a phone, 89% use smart phones. The majority of these users live in the 1st study area, Grabouw, and are the majority who engage with activities on their phones including watching videos, playing online games and listening to music.

Discussion

The main strength of this study is its longitudinal prospective design providing the possibility to determine the varying effect of the pesticide exposure, media use and other exposures over different time points. This study also collected detailed objective exposure data on current used agricultural pesticides obtained from urine and hair bio-monitoring, as well as environmental passive air and water sampling in the study areas. This exposure data will enable us to characterise and quantify

gression model on a continuous scale (linear/ordinal), will be considered whenever possible. The form of the exposure-response relationships will be explored using polynomial terms or non-parametric approaches (splines). In supplementary analyses, outcomes will be

the level of exposure of the participants and assess their cumulative exposure over the follow-up period.

By combining the biomonitoring with spraying schedules and detailed questionnaire data, a better understanding of critical behaviours for pesticide exposure will be obtained. All study areas are economically important farming areas with intensive use of pesticides, where pesticides have been detected previously and from theresults we have attained an equal distribution of partici- pants across these areas. By selecting three different areas where several types of farming products are cultivated, the study offers the possibility to compare the effects of differ- ent types and mixtures of pesticides. The study includes almost half of participants from farms compared to chil- dren not living on a farm, yielding variations in levels of exposure amongst the cohort. Useful exposure contrasts within the cohort is also demonstrated in other items of the baseline survey, such as seeing spraying activities and engaging with pesticide equipment which was reported by a few participants. About a third of the participants do en- gage with media use in all three areas, even though these are low income rural areas. Thus, the cohort is well suited to study the effects of uptake of media in adolescence.

The study population has an appropriate age range that includes children in various stages of development which will enable the researchers to investigate the changes in periods of pubertal and neurobehavioral development amongst the distinct groups of exposed children over the two-year period.

Development stage is assessed using standardised methods and complemented with a wide range of hormonal measurements indicative of reproductive development obtained from blood samples. Use of a validated computerised tool to measure neurobehaviour is a further asset of this study. This is the first iPad based study on this topic in a rural setting which will yield evidence of standardizing quality data and reliability for future studies on a large scale. Additionally, the questionnaires are comprehensive for collecting data on children's diet, socio-economic status, prenatal exposures and family environment to determine any influencing factors on behavior and development. The generation of exposure indices and the area of residence will help in understanding the patterns of lifetime exposure in relation to different environmental factors for e.g. proximity to spraying area.

Furthermore, by including co-exposures, pesticide effects can be studied independent of e-media and alcohol consumption, while synergistic effects can be studied.

Lastly this study carries power for attaining its objectives and methods with the use of a 1000 sample population.

Results from this study will be used to educate the community and government sectors involved in pesticide use and regulation. Suggestions that arise from this study will provide farming communities with awareness of health pro- motion and prevention strategies. In conclusion the find- ings from this study can contribute to the improvement and protection of children's health and development locally and internationally as these pesticides are used globally. This will be the first longitudinal study investigating the re- productive health effects on children of agricultural pesti- cides in current use and will seek to address conflicting results from studies investigating neurobehavioural effects.

Table 2 Description of the study population

	Area 1 Grabouw n (%)	Area 2 Piketberg n (%)	Area 3 DeDoorns n (%)	Total n (%)
No. of participants	325(32.5)	303 (30.3)	373 (37.2)	1001(100)
Age categories				
9-11 years	194(59.7)	223(73.6)	175(46.9)	592(59.1)
12-14 years	116(35.7)	79(26.1)	161(43.2)	356(35.6)
15-16 years	15(4.6)	1(0.3)	37(9.9)	53(5.3)
Gender				
Female	170(52.3)	159(52.5)	199(53.4)	528(52.7)
Male	155(47.7)	144(47.5)	174(46.6)	473(47.2)
No. of schools Grade categories	3 (42.8)	2 (28.6)	2 (28.6)	7 (100)
2nd-3rd	37(11.4)	77(25.4)	49(13.1)	163(16.3)
4th-6th	235(72.3)	210(69.3)	222(59.5)	667(66.6)
7th-9th	53(16.3)	16(5.3)	102(27.3)	171(17.1)
Current Farm resident Occupation	202(62.2)	121 (39.9)	142 (38.1)	465(46.4)
Family member works on a farm	199(61.2)	180 (59.4)	281 (75.3)	660(65.9)
Pesticide activities				
Seen pesticide spraying activities in nearby field	278(34.6)	233(76.9)	291(78)	802(80.1)
Helped with cleaning farm equipment	63(85.5)	63(20.8)	97(26)	223(23.2)
Assisted with pesticide storage in the past 7 days	65(20)	49(16.2)	92(24.7)	206(20.5)
Social Media use				
Use a mobile phone	187(57.5)	63(20.8)	68(18.2)	318 (31.7)
Use a smart phone	176(54.2)	48(15.8)	60(16.1)	284(28.4)
Connect to the internet to watch videos	112(34.5)	16(5.9)	17(4.6)	145(14.5)
Connect to the internet to play online games	101(31.1)	6(2)	17(4.6)	124 (12.4)
Connect to the internet to listen to music	111(34.2)	13(4.3)	21(5.6)	145 (14.5)

Abbreviations

ADHD: Attention Deficit Hyperactivity Disorder; ASD: Autism Spectrum Disorder; CANTAB: CAmbridge Neuropsychological Test Automanted Battery; CEM: Crop-exposure matrices; DAFF: Department of Agriculture, Forestry and Fisheries; EDC: Endocrine Disrupting Chemical; FASD: Fetal Alcohol Syndrome Disorder; HIT-6: Headache Impact Test-6; ODK: Open Data Kit; PDD: Pervasive Developmental Disorders; PUF-PAS: Polyurethane foam disks;
SDB: Styrenedivinylbenzene; WHO: World Health Organisation; XAD-PAS: XAD resin

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Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to confidentiality and anonymity of the learners and their guardians. The datasets are stored on a secure Alfresco website and are available from the authors and to the co-authors on reasonable request.

Authors' contributions

AD and MR are the principal investigators of the study and contributed to the design, methods, funding and topics in the protocol and writing of the manuscript. SM is responsible for writing up the first draft and editing of the protocol paper during its development toward the final version, baseline data monitoring, the descriptive analysis, establishing the methods and training for the cognitive assessment and development of the questionnaires. WB and SF developed the SOPs and coordinated the cohort study. SF was responsible for the methods of the water and air sampling and the farm-owner questionnaire. WB developed the reproductive and pesticide bio-monitoring and exposure questionnaire aspects of the proposal and was responsible for the methods of the reproductive health outcome. MM and JVW and SD are responsible for the laboratory analysis of hair, urine and blood samples for the study. They contributed to the section on pesticide biomonitoring and sample testing in this paper. NP and the above authors read and provided comments for the protocol draft. All authors have read and approved the final version of the protocol paper.

Ethics approval and consent to participate

Parents or guardians of the participants as well as farm-owner were required to provide signed permission to be a part of this study and written consent. The participant learner were required to provide written assent once their parent's consent was received and before any data was collected. Primary ethical principles based on the Helskinki Declaration [51], will be considered for the benefit and protection of subjects in this study.

The ethical protocols for the study on pesticide exposure and reproductive health outcomes has been approved by the University of Cape Town's

Human Research Ethics Committee (HREC reference number: 234/2009). An amendment was made to this protocol for the addition of neurobehavioral outcome and submitted for ethical clearance, which was approved on May 2017 by the University of Cape Town's Human Research Ethics Committee (reference: 234/2009). The Ethics Committee of the Northwest and Central Switzerland (EKNS) reviewed and confirmed ethical and scientific standards of the study in November 2017 (reference: EKNS 2017–01683). The Western Cape Education Department has provided approval and consent to conduct this study amongst the children who attend school in these study areas (reference: 20150629–846). An additional ethical protocol for the farm-owner questionnaire and the environmental assessment was approved by HREC on the October 2017 (reference number: 597/2017).

Consent for publication

"Not applicable"

Competing interests

The authors declare that they have no competing interests in this study.

Publisher's Note

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Chapter 3

3. Electronic media use and neurobehvaior

Different aspects of electronic media use, symptoms and neurocognitive outcomes of children and adolescents in the rural Western Cape region of South Africa

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Different aspects of electronic media use, symptoms and neurocognitive outcomes of children and adolescents in the rural Western Cape region of South Africa

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ABSTRACT

Background: Electronic media use is increasing in low- and middle-income countries, thus we aim to investigate the prevalence of different aspects of e-media use and its association to symptoms and neurocognitive outcomes in rural South Africa.

Methods: In the cohort study, "Child health Agricultural Pesticide study in South Africa (CapSA)", of 1001 children and adolescents, aged 9–16 years, we enquired at baseline about the following aspects of e-media use: (1) call duration (2) total screen time (3) night-time awakenings from mobile phone use, and (4) Mobile Phone Problematic Use. Four health outcomes were included: sleep disturbance, health related quality of life (HRQoL), headaches and cognitive performance, assessed through six tests on domains of attention, memory and processing speed, using the iPad-based software, CAmbridge Neuropsychological Test Automated Battery (CANTAB). Linear regression analysis adjusted for relevant confounders was conducted with categorized exposure variables low, medium and high use.

Results: One third of the cohort (31.8%) are mobile phone users reporting average duration of calls per day up to 75 min (mean = 2.5 mins; SD = 8.9 mins). Amongst 46% of the cohort who report e-media device use, total screen time ranged from 1 min to 441 min (mean = 28.3; SD = 53.0). *Findings* Amongst those reporting regular night-time awakenings (≥1 times per week) from mobile phones, HRQol declined by 2.9 (95% CI: −6.1, 0.3), the sleep disturbance score increased by 2.0 (1.1, 2.9) units and headache impact score significantly increased by 5.4 (2.6; 8.2) units compared to non-exposed. Cognitive performance scores tended to be slightly improved mostly in moderate e-media users. The reaction response speed was consistently improved amongst all four exposure groups compared to non-users.

Conclusion: These results are among the first from Africa on benefits and risks associated with e-media use. Our findings imply that with regard to the education of adolescents, a vigilant balance is needed to profit from the beneficial effects of moderate e-media use on cognition, while preventing the negative side effects for HRQoL, sleep disturbance and headache severity.

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3.1 Introduction

There is a known 'digital divide', delaying the availability of internet access and affordability in Africa and developing countries, compared to the global internet context.[56] However, South Africa, a Low to Middle Income Country (LMIC) has 150 mobile phone subscriptions per 100 people compared to 91 in LMIC's and 42% of its population are internet users since 2017[57]. These rates are comparable to certain EU and North American contexts, although access and usage is considerably lower in rural areas of South Africa.[58 59 60] So far little research has been conducted on e-media use in African settings with low prevalence of mobile phone and e-media use among adolescents and thus it remains unclear whether findings from high income countries apply to such settings as well.

Research in high income countries shows that the highest users of e-media and screen time (including smart phones, computers and tablets) are the youth, spending several hours a day for activities including movie watching, text messaging, talking on the telephone, listening to music and playing online games.[61]The World Health Organization (WHO) recognizes the educational and social benefits of engaging with e-media but distinguishes that e-media becomes problematic when negative health symptoms become apparent.[62] The WHO refers to this problematic use as excessive use of e-media, which is associated with behavioral disorders or addictions and consequent health effects. Observed health implications are poor quality of life,[63] headaches,[48] sleep disturbances,[64,65,66] anxiety,[67] depression,[68] and cognitive dysfunction[69] including impulsivity.[62,70,71] Evidence on health-related problems from e-media use conclude there is more impact from problematic behavior of e-media use than radiation exposure from e-media use, although the latter has also been explored in many studies.[72] However, problematic behavioral use is poorly defined in reference to excessive e-media use, it is generally referred to in dimensions of over-use, misuse and dependency when measuring problematic mobile phone use.[73]

Since e-media use may be related to various lifestyle aspects, observed associations of e-use with neurocognitive outcomes are therefore less well understood globally. We are interested in exploring the pattern of e-use in a cohort of adolescents from three rural areas located in one province in South Africa. In particular, we aim at investigating four different behavioral aspects of e-media use and its association to non-specific health symptoms: 1.) duration of phone calls 2.) duration of screen-time 3.) mobile phone related night-time awakenings, and 4.) problematic mobile phone use capturing aspects of addiction and preoccupation with mobile phones as assessed by the Mobile Phone Problematic Use Scale (MPPUS-10). We investigate associations of these behaviors in relation to headaches, sleep disturbance and HRQoL as well as cognitive performance including processing speed, attention and memory capacity of adolescents.

3.2 Method

Study Design and ethics

Imbedded within the CapSA (Child health Agricultural Pesticide study in South Africa) longitudinal cohort study on agricultural pesticide exposure, neurobehavioral and reproductive health outcomes, this is a cross-sectional analysis on the baseline data, from the 1001 children and adolescent participants between the ages of 9-16 years who were voluntarily recruited from seven consenting schools across three rural agricultural areas of the Western Cape province in South Africa, DeDoorns, Piketberg and Grabouw. [74] We included public schools with similar population mix, who voluntarily participated, as described in the protocol paper. Of the 32 existing schools in all three study areas, only primary, intermediate and combined schools were contacted to prevent loss to follow-up (i.e., children and adolescents from high schools would have left school before the follow-up examination in 2019). Of the 22 intermediate schools, 12 were willing to participate and four of the seven combined schools were willing to participate. The principals and governing bodies of these 16 schools were contacted and informed about the study and seven agreed to participate[23].

The ethical protocol for the CapSA study was approved by the University of Cape Town's Human Research Ethics Committee (HREC REFERENCE NUMBER: 234/2009) in August 2016 -. The Ethics Committee of the Northwest and Central Switzerland (EKNS) reviewed and confirmed ethical and scientific standards of the study in November 2017 (reference: EKNS 2017-01683). Baseline data was collected in 2017 through interviews and assessments with adolescents during school hours.

The following questionnaires were conducted during school hours electronically by trained interviewers using Open Data Kit (ODK) applicationon a mobile phone:

2.1.1 Exposure measures

To ascertain e-media use, we administered a questionnaire about type (mobile phone, smart phone, computer, laptop, table PC (iPad, Tablet etc) and frequency (average minutes per day) of e-media usage including frequency of internet activities (watching videos, reading the news or other sites, being active on social media, playing online games) on mobile phones (See supplementary, Table 1).

The following four exposure variables were used and derived from the questionnaire (refer to Supplementary, Table 1, for additional information on each exposure question):

1. The length of calls with a mobile phone on average per day.
2. Total screen time per day derived from the sum of minutes spent on mobile phone internet activities (watching videos, reading news and other internet sites, being active on social media e.g. Facebook, Snapchat, Instagram, Musicaly, playing online games,) with device use (computer, laptop and or tablet use) and texting.
3. Night-time mobile phone awakenings by the reported number of times woken up per week.
4. Problematic mobile phone use and related dependency patterns were inquired in all subjects

who indicated the use of a mobile phone by completing the Mobile Phone Problem Use Scale-10 (MPPUS-10)[75] a shorter version adapted from the MPPUS-27.

2.1.2 Health Outcomes

Four types of health outcomes were measured using the following tools:

1. Sleep disturbance was measured from responses to four standardised questions using the Swiss Health Survey on difficulties with falling asleep, restless sleep, involuntary awakenings and too early morning awakenings, then summed as a continuous total score.
2. HRQoL was measured using the shortened KIDSCREEN-10 questionnaire with a five point Likert scale on wellbeing in the areas of physical, psychological, relational support and school environment, then summed as a continuous total score.
3. Headaches were screened for, using the six-item Headache Impact Test (HIT-6), which assesses the severity of headaches, and summed as a continuous total score.
4. Cognitive performance on three cognitive domains: processing speed, memory and attention were assessed using the neurocognitive battery, CANTAB (refer to protocol paper for details on the design).[74] Two CANTAB tests per domain measures cognitive performance by recording several performance scores, including latency and accuracy for each task within each test (see Supplementary, Table 5 for test names and description). Continuous data scores from the CANTAB were transformed to the closest normal distribution. The latency scores in milliseconds per task were inversed to a speed measure. Inaccuracy scores were converted to accuracy scores for consistent result presentation. Outliers were excluded if any value was 3.25 standard deviations above and below the mean (Supplementary, Table 3).

Statistical Analysis

Binary variables (yes/no) were created for those who reported e-media use and engage with e-media activities and those who do not, to determine variation patterns amongst users and non-users with demographic variables using Chi squared tests at a significance level ($p<0.05$).

All exposure variables were categorized in three exposure groups (no, low, high). For screen time and problematic mobile phone use score, we used a median split of all exposed participants resulting in a cut-off value of 55 minutes and 36 units, respectively. The categories for categorical exposure questions are shown in Figure 1 and 3. We conducted linear regression modelling to express changes in outcomes scores for low and high exposed study participants in comparison to non-exposed, adjusted for several co-variates. We further conducted separate analyses for the children (<12 years) and the adolescents (≥12 years).

2.2.1 Covariates

As co-variates we included age, sex and area of residence, living on a farm and substance abuse (drugs, alcohol and smoking). Further, we added to the model whether somebody had ever experienced a head injury and its severity if any, as this may be related to the outcomes and to exposure related lifestyle.

In explorative analysis we found some indication that mobile phone ownership is a strong proxy for socio-economic status. Thus, we conducted additional analysis, where we adjusted the models for screen time and night-time awakening for mobile phone ownership as well. Since mobile phone ownership showed high collinearity with call duration and mobile phone problematic use, corresponding models were not adjusted. Further socio-demographic variables were available from a guardian interview of 482 study participants. Thus, to explore the relevance of socio-demographic confounders, we conducted additional analyses in this subgroup adjusting for maternal employment, maternal education, home language, household size and Government grant. To receive subsidization by a Government grant is indicative of a low socioeconomic status.

Using continuous outcome variables, linear multivariable regression models were performed to evaluate associations between exposure and health outcome variables adjusted for covariates.

All analyses were done using Stata/IC 14.0 software.

3.3 Results

Table 1: Demographic variables and potential covariates across e-media and non e-media users in this cohort. For exposure groups row percentages are shown.

Demographic variables	N total (%)	N sub-group[2] (%)	Mobile phone Users (%)	Chi² *p-value*[1]	Smart phone Users (%)	Chi² *p-value*[1]	Laptop Users (%)	Chi² *p-value*[1]	Computer Users (%)	Chi² *p-value*[1]	Tablet Users (%)	Chi² *p-value*[1]
Gender												
Male	473(47)	231(52)	155(33)	*0.52*	138(29)	*0.60*	138(29)	*0.90*	63(13)	*0.13*	105(22)	*0.50*
Female	528(53)	251(48)	163(31)		146(28)		61(12)		54(10)		108 (21)	
Age												
9-11	592 (59)	284 (59)	173 (29)	*0.10*	149 (25)	*0.02*	76 (13)	*0.20*	75 (13)	*0.30*	140 (24)	*0.04*
12-14	356 (36)	164 (34)	124 (35)		116 (33)		34 (10)		34 (10)		67 (19)	
15-16	53 (5)	34 (7)	21 (40)		19 (36)		4 (8)		8 (15)		6 (11)	
Area												
Grabouw	325 (33)	105 (22)	187 (58)	*<0.01*	176 (54)	*<0.01*	53 (16)	*<0.01*	49 (15)	*0.01*	100 (31)	*<0.01*
Piketberg	303 (30)	139 (29)	63 (21)		48 (16)		40 (13)		42 (14)		74 (24)	
DeDoorns	373 (37)	238 (49)	68 (18)		60 (16)		21 (6)		26 (7)		39 (10)	
Head Injury												
none	659 (66)	304 (63)	230 (35)	*0.01*	204 (31)	*0.03*	62 (9)	*0.01*	66 (10)	*<0.01*	140 (21)	*0.68*
head accident	230 (23)	116 (24)	61 (26)		57 (25)		32 (14)		26 (11)		46 (20)	
(potential TBI)	112 (12)	62 (13)	27 (24)		23 (21)		20 (18)		25 (22)		27 (24)	
Smoke												
No	854 (85)	410 (85)	288(34)	*<0.01*	257(30)	*<0.01*	86 (10)	*<0.01*	98(11)	*0.61*	193 (23)	*0.01*
Yes	147 (15)	72 (15)	30(20)		27 (18)		28 (19)		19 (13)		20 (14)	
Alcohol												
No	851 (85)	395 (82)	286 (34)	*<0.01*	257(30)	*<0.01*	96 (11)	*0.80*	104 (12)	*0.21*	659 (77)	*0.02*
Yes	150 (15)	87 (18)	32 (21)	*0.10*	27 (18)		18 (12)		13 (9)		192 (23)	
Drugs												
No					280 (29)	*0.20*	113 (12)	*0.24*	116 (12)	*0.23*	210 (22)	*0.30*
Yes	976 (98)	468 (97)	314 (32)		4 (16)		1 (4)		1 (4)		3 (12)	
	25 (2)	14 (3)	4 (16)	*0.20*								
Farm Residence												
No			211 (30)		189 (27)	*0.30*	82 (12)	*0.50*	84 (12)	*0.51*	162 (23)	*0.01*
Yes	692 (69)	364 (75)	107 (35)		95 (31)		32 (10)		33 (11)		51 (17)	
	309 (31)	118 (25)										
Total N (%)	1001 (100)	482 (100)	318 (31.8)		284(28.4)		114 (11.4)		117 (11.7)		213 (21.3)	

[1]Chi² square test (p<0.05), differences between user and non-user groups and corresponding demographic variable
[2] Subroup with demographic variables from quardian interviews

We assessed a total of 1001 children and adolescents aged 9-16 years (mean: 11; SD: ±1.7) in grade 2 to 9 (5; ±1.5) distributed almost equally over three rural areas (Table 1). 318 (31.8%) Use a mobile phone for calls, texting or the internet; 284 (28%) have smartphones; 350 (35%) are e-media device users including 114 participants (11%) using laptops; 117 (12%) use computers; and 213 (21%) use tablets. Of the potential lifestyle covariates, around 30% of the cohort live on an agricultural farm compared to a nearby town area. Regarding covariates 34% reported a head injury, 15% report smoking, 16% report alcohol and 2% other drug consumption.

In this rural context of South Africa, poverty is rife, knowing that amongst the subset of 482 where the guardian questionnaire was completed (Supplementary, Table 7 for sociodemographic variables), almost 70% are recipients of child support grants, meaning they earn within the lowest income salary bracket and a further 22% are in receipt of other government grant support. The unemployment rate among mothers is 36% and 41% of them have less than or no primary education. Furthermore, 38% of the households in the subset have 5-6 members, while 24% of households have seven or more members residing in one house.

Mobile phone usage increased in age from 29% in the youngest age group (9-11 year olds) to 35% amongst 12-14 years olds and 40% in the oldest age group (15-16 year olds). The majority of mobile phone users (58%) live in the Grabouw area, which is closer to the city of Cape Town than the other two areas. The distribution of usage amongst moderate and high exposure groups is displayed in the Figures 1 to 4 and stratified by sex in Supplementary, Table 4, with no differences between males and female use observed. Seventy two percent of the cohort do not make phone calls on a daily basis, 19% call on average between 1 to 5 minutes per day, while 9% call between 6 and 75 minutes a day (Figure 1). Fifty four percent of the cohort do not engage in screen time activities, while 25% spend 55 minutes or less on screen time, and 21% spend longer than average of 55 minutes on screen time per day (Figure 2). Eighty six percent of the cohort do not get woken up at night by their mobile phones, while 14%, almost half of mobile phone users, are woken up at night by a call or message from their phone at least once a week (Figure 3). Figure 4 shows the distribution of the MPPUS-10. A score of 0 indicates no mobile phone use.

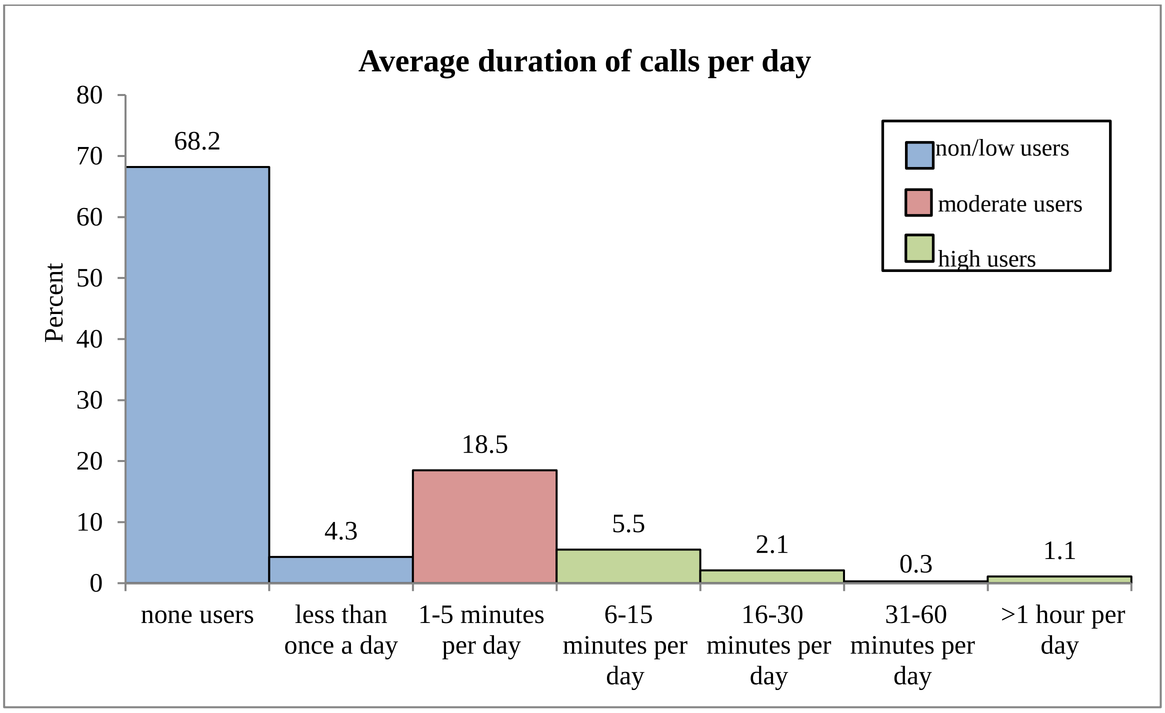

Figure 1: Response categories and proportion of responses for the variable duration of mobile phone calls per day

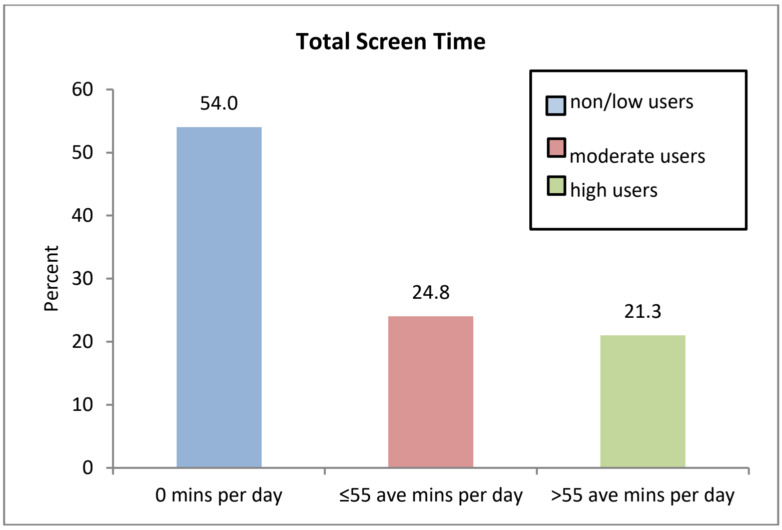

Figure 2: The distribution in average minutes of total screen time users amongst mobile phone users only

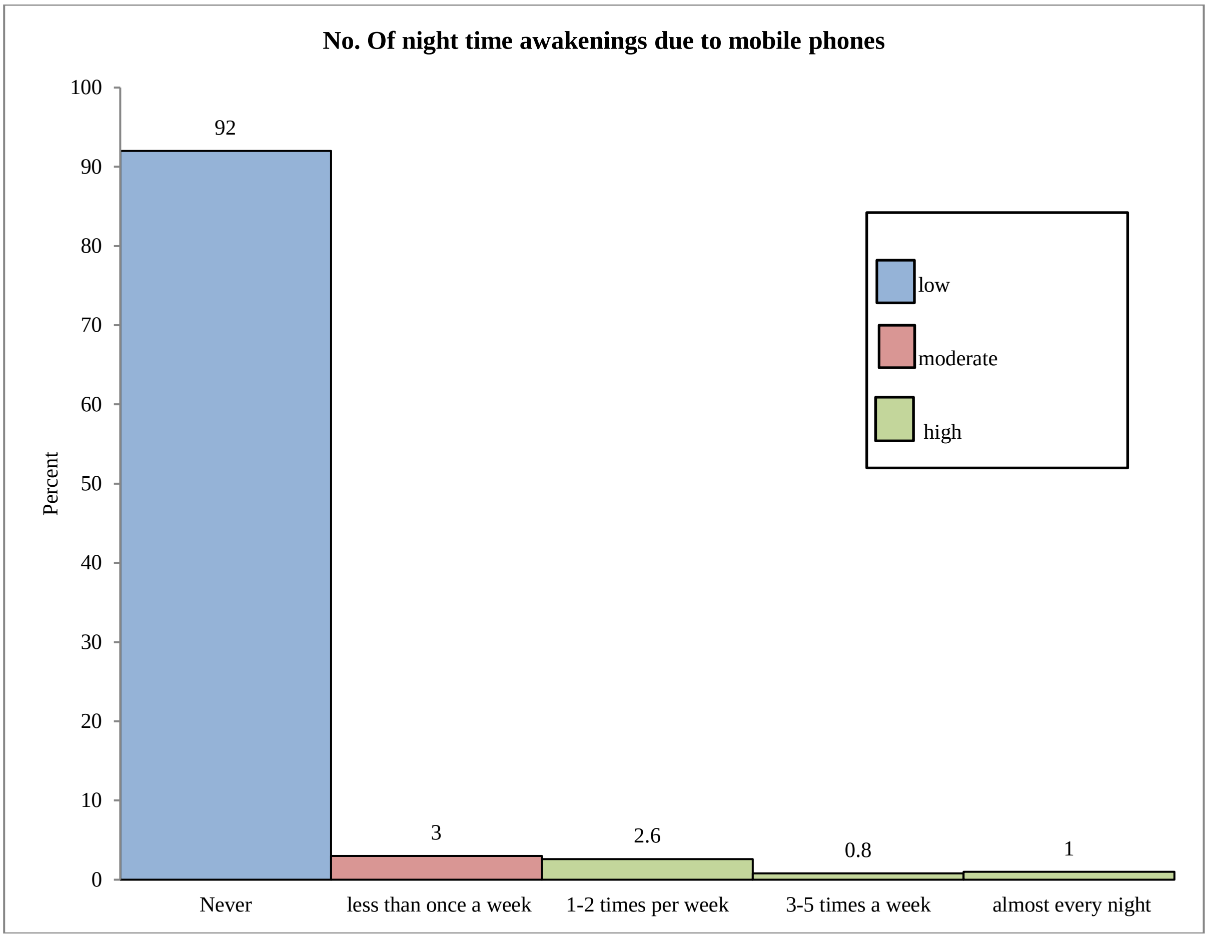

Figure 3: Response categories and proportion of responses for the variable on night time awakenings from mobile phone use in the whole cohort

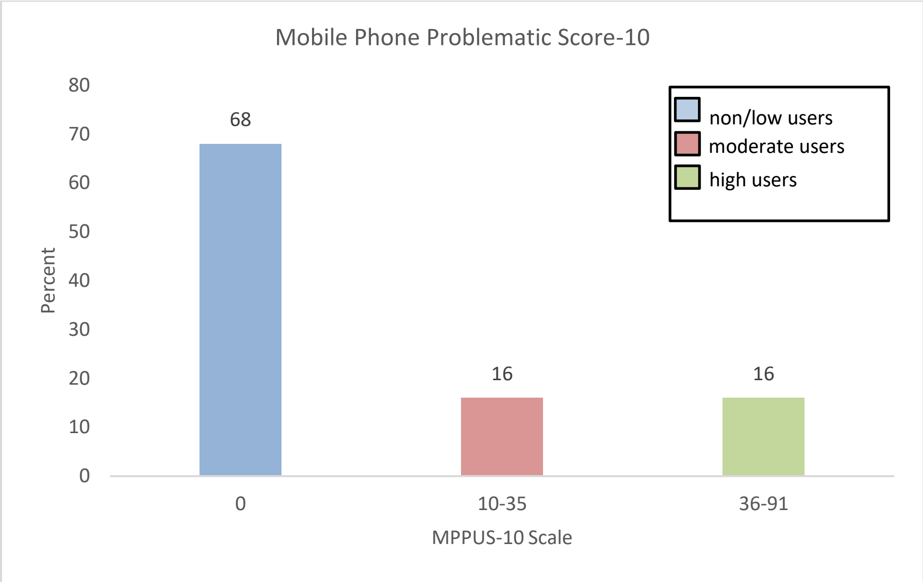

Figure 4: The distribution of the Mobile Phone Problematic Use Score (MPPUS-10) amongst mobile phone users only

Table 2: Linear regression analysis results - change in health score for study participants belonging to the medium or high exposure group with respect to e-media use, duration of mobile phone calls and screen time. Significant estimates (p<0.05) are printed in bold.

Symptoms	n	Duration of calls n=185 (medium); 90 (high)		Screen Time n=248 (medium); 213 (high)		Mobile phone related awakenings n=30 (medium); 44 (high)		Mobile phone Problematic use n=159 (medium); 159 (high)	
		Crude [95%CI]	Adjusted (95%CI)	Crude [95%CI]	Adjusted* [95%CI]	Crude [95%CI]	Adjusted* [95%CI]	Crude [95%CI]	Adjusted [95%CI]
Sleep disturbance	998								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Medium		-1.30 (-1.71; -0.89)	-0.92(-1.36; -0.48)	-0.71 (-1.13;-0.28)	-0.16 (-0.64; 0.33)	-0.56 (-1.59; 0.46)	-0.31 (-0.72; 1.35)	-2.25 (-2.72; -1.78)	-1.86 (-2.38; -1.34)
High		1.77 (0.82; 2.72)	1.92 (0.98; 2.87)	-0.39 (-0.84; 0.06)	-0.19 (-0.35; 0.73)	1.31 (0.45; 2.18)	2.02 (1.14; 2.91)	0.28 (-0.18; 0.75)	0.39 (-0.08; 0.88)
HRQoL	1001								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	00 (ref)	0 (ref)
Medium		6.91 (5.45; 8.36)	5.70 (4.09;7.31)	4.64 (3.12;6.17)	1.59 (-0.17; 3.35)	5.39 (1.64; 9.16)	0.29(-3.47; 4.07)	9.55 (7.86; 11.23)	8.50 (6.63; 10.37)
High		2.75 (-0.62; 6.13)	1.77 (-1.64; 5.18)	4.39 (2.79; 5.99)	0.64 (-1.30; 2.58)	1.79 (-1.32; 4.92)	-2.86(-6.05; 0.33)	33.50 (1.81; 5.18)	2.87 (1.12; 4.62)
Headaches	999								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	00 (ref)	0 (ref)
Medium		-6.38 (-7.71; -5.06)	-4.83 (-6.25;-3.41)	-4.05 (-5.45; -2.66)	-0.59 (-2.14; 0.97)	-1.67 (-5.10; 1.77)	2.95 (-0.36; 6.27)	--11.36(-12.83; 9.89)	-9.89 (-11.48; 8.29)
High		-1.76 (-4.87; 1.36)	-0.85 (-3.91; 2.21)	-2.97 (-4.45; -1.49)	0.76 (-0.96; 2.48)	0.84 (-2.02; 3.70)	5.37 (2.56; 8.17)	- -0.71 (-2.19; 0.76	-0.17 (-1.67; 1.33)

Adjusted = sex, age, area, head injury, smoke, alcohol, drugs, farm residence
**Adjusted+mobilephone ownership (binary)*

Symptoms	n			Total Screen Time n=108 (medium); 90 (high)		Mobile phone related awakenings n=21 (medium); 19 (high)		Mobile phone Problematic use n=57 (medium); 75 (high)	
		Adjusted (95%CI)	Adjusted 1 (95%CI)	Adjusted* (95%CI)	Adjusted 1* (95%CI)	Adjusted (95%CI)	Adjusted 1* (95%CI)	Adjusted (95%CI)	Adjusted 1 (95%CI)
Sleep disturbance	482								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Medium		-1.43 (-2.19; -0.67)	-1.30(-2.08; -0.52)	-0.25 (-0.97; 0.46)	-0.27 (-0.99; 0.45)	0.96 (-0.36; 2.29)	0.96 (-0.37; 2.29)	-1.93 (-2.76; -1.10)	-1.78 (-2.62; -0.93)
High		0.02 (-0.92; 0.95)	0.07 (-0.88; 1.01)	-0.07 (-0.93; 0.79)	-0.01 (-0.88; 0.86)	2.09 (0.70; 3.48)	2.12 (0.73; 3.51)	-0.13 (-0.86; 0.59)	-0.70 (-0.81; 0.67)
HRQoL	482								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Medium		7.73 (5.06; 10.40)	7.63 (4.92; 10.33)	2.42 (-0.07;4.90)	2.45 (-0.03;4.92)	-0.36 (-5.02; 4.23)	-0.39 (-5.02; 4.24)	9.69 (6.81; 12.58)	9.57 (6.65; 12.49)
High		4.00 (0.73; 7.28)	4.34 (1.06; 7.62)	1.42 (-1.57; 4.41)	1.87 (-1.13; 4.87)	-2.99 (-7.86; 1.88)	-2.71 (-7.54; 2.13)	3.52 (0.98; 6.06)	3.67 (1.12; 6.23)
Headaches	482								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Medium		-7.32 (-9.72; -4.91)	-7.48(-9.95; -5.01)	-0.25 (-2.50; 2.00)	-0.29(-2.57; 1.99)	3.31 (-0.88; 7.51)	3.44 (-0.79; 7.67)	-11.00 (-13.54;-8.46)	-11.18 (-13.77;-8.58)
High		-0.80 (-3.74; 2.15)	-0.78 (-3.78; 2.21)	0.01 (-2.71; 2.72)	-0.03 (-2.79; 2.73)	2.94 (-1.45; 7.32)	2.99 (-1.43; 7.41)	-1.41 (-3.65; 0.82)	-1.49 (-3.77; 0.79)

Table 3: Linear regression analysis results - change in health score for sub-set study participants belonging to the medium or high exposure group with respect to e-media use, duration of mobile phone calls and screen time and adjusted for SES. Significant estimates (p<0.05) in bold.

Adjusted = sex, age, area, head injury, smoke, alcohol, drugs, farm residence
**Adjusted+mobilephone ownership (binary)*
Adjusted 1 = Adjusted+mother employment, mother education, home language, household size, government grant, repeated grade
**Adjusted 1+mobilephone ownership (binary)*
Data presented as the Beta from linear regression models

Table 2 shows the score changes for various symptoms in relation to various exposure variables. Compared to non-exposed inviduals the sleep disturbance score is significantly elevated among high mobile phone users and those woken up during night at least three times a week. No association for screen time and problematic mobile phone use was found, whereas medium mobile phone use and medium problematic use was associated with a lower sleep disturbance score. HRQoL was positively associated with mobile phone ownership and moderate use, possibly reflecting sociodemographic confounding. . After adjusting for mobile phone ownership screen time was not associated with HRQoL and high number of mobile phone related awakenings tended to be associated with lower HRQoL, unmasking the positive health effect associated with mobile phone ownership status. The same pattern was seen for headache. After adjusting for mobile phone ownership headache was not associated with screen time and increased among those regularly woken up from a mobile phone.
Mobile phone ownership could not be added to the models of MPPUS-10 due to high correlation and thus corresponding associations should be interpreted with caution as they may reflect associations with mobile phone ownership. Similar results were found in a subgroup analysis with additional sociodemographic variables (Table 3). Note, home language and maternal education were significant predictors of HRQoL for all four exposure models (coefficients not shown).

Table 4: Linear regression analysis results - change in cognitive performance score for study participants belonging to the medium or high exposure group with respect to e-media use, duration of mobile phone calls, screen time and mobile phone awakenings. Significant estimates (p<0.05) are printed in bold. Refer to Supplementary, Table 5, for test name and description in each domain.

Neurocognitive Outcomes	n	Duration of calls n=185 (medium); 90 (high)		Screen Time n=248 (medium); 213 (high)		Mobile phone related awakenings n=30 (medium); 44 (high)		Mobile phone Problematic use n=159 (medium); 159 (high)	
		Crude (95%CI)	Adjusted (95%CI)	Crude (95%CI)	Adjusted* (95%CI)	Crude (95%CI)	Adjusted* (95%CI)	Crude (95%CI)	Adjusted (95%CI)
PROCESSING SPEED									
MS Speed (seconds)	997								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate		0.02 (-0.04; 0.08)	0.01 (-0.05; 0.07)	0.05 (-0.01; 0.11)	0.05 (-0.02; 0.12)	0.07(-0.08; 0.21)	0.05 (-0.10; 0.20)	0.01 (-0.06; 0.08)	0.00 (-0.07; 0.08)
High		-0.04 (-0.18; 0.09)	-0.04 (-0.18; 0.09)	0.06 (-0.01; 0.12)	0.05 (-0.02; 0.13)	0.03(-0.09; 0.15)	0.01(-0.12; 0.14)	0.04 (-0.03; 0.11)	0.04(-0.03; 0.11)
RR Speed (seconds)	961								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate		0.19 (0.03;0.35)	0.17 (0.00; 0.35)	0.19 (0.02; 0.36)	0.16 (-0.04; 0.35)	0.27 (-0.13; 0.67)	0.26 (-0.14; 0.67)	0.01 (-0.18; 0.19)	-0.06 (-0.27; 0.15)
High		0.01 (-0.37; 0.39)	-0.05 (-0.43; 0.32)	0.29 (0.11; 0.46)	0.25 (0.04; 0.46)	0.48 (0.15; 0.81)	0.44 (0.09; 0.79)	0.22 (0.03; 0.41)	0.17 (-0.02; 0.37)
ATTENTION									
RVP speed (seconds)	981								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate		0.03 (-0.07; 0.15)	0.06 (-0.06; 0.18)	0.19 (0.08; 0.29)	0.22 (0.10; 0.36)	0.12 (-0.15; 0.38)	0.05 (-0.23; 0.33)	0.09 (-0.04; 0.22)	0.14 (-0.00; 0.28)
High		0.11 (-0.14; 0.37)	0.09 (-0.16; 0.35)	0.11 (0.00; 0.23)	0.16 (0.02; 0.30)	-0.02 (-0.24; 0.21)	-0.10 (-0.34; 0.14)	0.07 (-0.06; 0.19)	0.08 (-0.06; 0.21)
RVP accuracy (hits)	984								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate		0.01 (-0.01; 0.03)	0.00 (-0.02; 0.02)	0.01 (-0.00; 0.03)	0.01 (-0.01; 0.03)	0.02 (-0.02; 0.06)	0.02 (-0.02; 0.06)	0.01 (-0.01; 0.03)	0.01 (-0.01; 0.03)
High		0.01 (-0.01; 0.04)	-0.01 (-0.03; 0.02)	0.01 (-0.00; 0.03)	0.00 (-0.02; 0.02)	-0.01 (-0.04; 0.02)	-0.01 (-0.04; 0.03)	0.01 (-0.01; 0.03)	-0.01 (-0.03; 0.01)
MTT speed (seconds)	986								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate		0.03 (-0.01; 0.07)	0.02 (-0.02; 0.06)	0.02 (-0.02; 0.06)	0.01 (-0.04; 0.05)	0.02 (-0.07; 0.12)	-0.01 (-0.11; 0.09)	0.02 (-0.02; 0.07)	0.02 (-0.03; 0.07)
High		0.05 (-0.04; 0.13)	0.02 (-0.06; 0.11)	0.03 (-0.01; 0.07)	0.01 (-0.03; 0.06)	0.08 (0.00; 0.16)	0.06 (-0.02; 0.14)	0.04 (-0.01; 0.08)	0.02 (-0.03; 0.06)
MTT accuracy (hits)	994								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate		7.00 (3.91; 10.10)	4.85 (1.55; 8.15)	1.44 (-1.55; 4.45)	0.34 (-2.92; 3.59)	3.65 (-3.20; 10.51)	1.91 (-5.17; 9.00)	4.23 (0.92; 7.55)	2.16 (-1.43; 5.75)
High		2.14 (-2.06; 6.34)	-0.14 (-4.35; 4.08)	2.17 (-0.10; 5.33)	1.19 (-2.17; 4.54)	1.36 (-4.33; 7.06)	-0.62 (-6.66; 5.42)	6.15 (2.84; 9.47)	3.71 (0.35; 7.06)
MEMORY									
PAL accuracy (hits)	969								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate		0.38 (-0.24; 1.00)	0.23 (-0.45; 0.91)	0.07 (-0.53; 0.67)	-0.02 (-0.69; 0.65)	0.39 (-1.02; 1.80)	0.33 (-1.13; 1.79)	0.02 (-0.65; 0.68)	-0.12 (-0.85; 0.61)
High		-0.11 (-0.95; 0.74)	-0.29 (-1.15; 0.57)	0.06 (-0.55; 0.68)	-0.12 (-0.80; 0.57)	-0.29 (-1.49; 0.90)	-0.49 (-1.74; 0.76)	0.46 (-0.21; 1.13)	0.28 (-0.40; 0.97)

SWM accuracy (hits)	991								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate		0.74 (-0.12; 1.60)	0.66 (-0.28; 1.61)	0.47 (-0.36; 1.29)	0.58 (-0.35; 1.51)	2.14 (0.21; 4.08)	2.01 (0.02; 4.03)	-0.07 (-0.99; 0.86)	-0.18 (-1.21; 0.84)
High		-0.12 (-1.29; 1.05)	-0.28 (-1.49; 0.92)	0.45 (-0.41; 1.30)	0.58 (-0.38; 1.53)	-0.23 (-1.86; 1.39)	-0.39 (-2.11; 1.34)	0.80 (-0.12; 1.72)	0.63 (-0.33; 1.59)
SWM strategy (hits)	991								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate		0.27 (0.04; 0.50)	0.35 (0.10; 0.60)	0.15 (-0.71; 0.37)	0.08 (-0.16; 0.33)	0.12 (-0.39; 0.63)	-0.05 (-0.59; 0.48)	0.14 (-0.10; 0.38)	0.23 (-0.39; 0.50)
High		0.10 (-0.21; 0.40)	0.14 (-0.17; 0.46)	0.08 (-0.15; 0.30)	0.03 (-0.22; 0.28)	0.13 (-0.30; 0.56)	-0.07 (-0.53; 0.38)	0.30 (0.05; 0.54)	0.33 (0.07; 0.58)

Adjusted = sex, age, area, head injury, smoke, alcohol, drugs, farm residence
**Adjusted+mobilephone ownership (binary)*
**Data presented as the Beta from linear regression models*
Motor Screening (MS); Reaction Response (RR); Spatial Working Memory (SWM); Paired Associate Learning (PAL); Multi-tasking (MTT); Rapid Visual Information Processing (RVP)

Overall, regression analysis in Tables 4 shows that there are some small positive to non-significant associations across all three domains of cognitive performance in relation to mobile phone use and screen time. Of the 11 significant adjusted results displayed across all four exposures, six improved scores were observed amongst moderate users and five amongst high users across all three domains in five specific cognitive areas, namely RR and RVP speed, MTT and SWM accuracy and SWM strategy score. Moderate users of mobile phone calls had improved across all three domains, specifically in the area of RR Speed, MTT accuracy and SWM strategy scores. Both moderate and high users of screen time displayed positive associations to RVP speed in attention and high users of screen time and mobile phone awakenings displayed an association to RR speed. Moderate problematic mobile phone users displayed a positive association to RVP speed in attention, while higher users had significantly improved MTT accuracy and SWM strategy scorese compared to non-users. The positive associations for MTT accuracy scores became lower and partly insignificant after adjusting, possibly indicating residual confounding for these test results. . Adjustment with additional SES factors (Table 5) yielded similar results, although with wider confidence intervals and thus number of significant associations was lower in this subgroup analysis..

Table 5: Linear regression analysis results - change in cognitive performance for sub-set study participants belonging to the medium or high exposure group with respect to e-media use, duration of mobile phone calls and screen time and adjusted for SES. Significant estimates (p<0.05) in bold. Refer to Supplementary, Table 5, for test name and description in each domain.

Neurocognitive Outcomes	n	Duration of calls n=72 (medium); 41 (high)		Screen Time n=108 (medium); 90 (high)		Mobile phone related awakenings n=21 (medium); 19 (high)		Mobile phone Problematic use n=57 (medium); 75 (high)	
		Adjusted [95%CI]	Adjusted 1 (95%CI)	Adjusted* [95%CI]	Adjusted 1* [95%CI]	Adjusted* [95%CI]	Adjusted 1* [95%CI]	Adjusted [95%CI]	Adjusted 1 [95%CI]
PROCESSING SPEED									
MS Speed (seconds)	458								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate		0.00 (-0.11; 0.11)	0.01 (-0.10; 0.13)	0.02 (-0.09; 0.12)	0.02 (-0.09; 0.12)	0.07 (-0.12; 0.26)	0.07 (-0.13; 0.26)	0.08 (-0.04; 0.20)	0.09 (-0.03; 0.22)
High		0.05 (-0.09; 0.19)	0.03 (-0.11; 0.17)	0.08 (-0.04; 0.21)	0.07 (-0.06; 0.20)	-0.16 (-0.36; 0.04)	-0.17 (-0.37; 0.03)	0.04 (-0.07; 0.15)	0.03 (-0.08; 0.14)
RR Speed (seconds)	458								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate		0.09 (-0.02; 0.38)	0.09 (-0.21; 0.39)	0.21 (-0.05; 0.48)	0.23 (-0.04; 0.50)	0.57 (0.08; 1.07)	0.56 (0.06; 1.06)	-0.07 (-0.39; 0.25)	-0.08 (-0.41; 0.24)
High		0.07 (-0.29; 0.43)	0.05 (-0.32; 0.41)	0.31 (-0.01; 0.64)	0.32 (-0.01; 0.64)	0.23 (-0.28; 0.75)	0.22 (-0.30; 0.74)	0.02 (-0.26; 0.30)	0.00 (-0.28; 0.29)
ATTENTION									
RVP speed (seconds)	472								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate		0.06 (-0.14; 0.26)	0.03 (-0.17; 0.23)	0.24 (0.06; 0.42)	0.24 (0.06; 0.42)	-0.15 (-0.36; 0.33)	0.00 (-0.34; 0.35)	0.25 (0.33; 0.47)	0.23 (0.01; 0.45)
High		-0.04 (-0.28; 0.21)	-0.02 (-0.27; 0.23)	-0.05 (-0.27; 0.17)	-0.06 (-0.28; 0.17)	0.08 (-0.29; 0.44)	0.09 (-0.28; 0.46)	0.02 (-0.17; 0.21)	0.03 (-0.16; 0.22)
RVP accuracy (hits)	472								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate		0.02 (-0.11; 0.49)	0.02 (-0.01; 0.05)	0.01 (-0.01; 0.04)	0.02 (-0.01; 0.04)	0.03 (-0.02; 0.08)	0.03 (-0.02; 0.08)	0.04 (-0.01; 0.07)	0.04 (0.00; 0.07)
High		0.00 (-0.04; 0.04)	0.00 (-0.04; 0.03)	0.02 (-0.02; 0.05)	0.02 (-0.02; 0.05)	-0.04 (-0.09; 0.02)	-0.04 (-0.10; 0.02)	-0.01 (-0.04; 0.02)	-0.01 (-0.04; 0.02)
MTT speed (seconds)	473								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate		-0.01 (-0.06; 0.04)	0.00 (-0.05; 0.06)	0.00 (-0.05; 0.05)	0.00 (-0.05; 0.05)	-0.02 (-0.11; 0.07)	-0.02 (-0.12; 0.07)	0.02 (-0.04; 0.08)	0.03 (-0.04; 0.09)
High		0.02 (-0.05; 0.08)	0.02 (-0.05; 0.09)	0.03 (-0.09; 0.03)	-0.03 (-0.09; 0.03)	0.06 (-0.04; 0.16)	0.05 (-0.05; 0.15)	0.00 (-0.05; 0.05)	0.00 (-0.05; 0.05)
MTT accuracy (hits)	473								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate		4.24 (-1.00; 9.48)	3.60 (-1.75; 8.95)	0.16 (-4.73; 5.06)	0.21 (-4.71; 5.13)	3.38 (-5.71; 12.46)	3.96 (-5.16; 13.07)	3.29 (-2.45; 9.04)	1.77 (-4.08; 7.63)
High		2.86 (-3.62; 9.34)	2.70 (-3.84; 9.25)	-2.37 (-8.26; 3.51)	-2.01 (-7.97; 3.94)	0.61 (-10.35; 9.13)	0.61 (-9.17; 10.39)	3.74 (-1.32; 8.81)	3.40 (-1.73; 8.53)
MEMORY									
PAL accuracy (hits)	457								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate		0.28 (-0.80; 1.36)	0.11 (-1.00; 1.22)	-0.35 (-1.35; 0.65)	-0.36 (-1.37; 0.65)	0.56 (-1.32; 2.44)	0.56 (-1.34; 2.45)	-0.05 (-1.22; 1.12)	-0.24 (-1.44; 0.96)
High		-0.39 (-1.70; 0.93)	-0.51 (-1.84; 0.83)	0.03 (-1.18; 1.25)	-0.05 (-1.29; 1.18)	-1.26 (-3.39; 0.86)	-1.22 (-3.37; 0.94)	0.18 (-0.86; 1.22)	0.06 (-1.00; 1.11)

SWM accuracy (hits)	457								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate		-0.29 (-1.80; 1.23)	-0.24 (-1.80; 1.32)	0.32 (-1.10; 1.71)	0.31 (-1.09; 1.72)	2.70 (0.07; 5.34)	2.75 (0.11; 5.39)	-1.30 (-2.93; 0.33)	-1.45 (-3.11; 0.21)
High		0.24 (-1.61; 2.09)	-0.10 (-1.96; 1.78)	1.88 (0.18; 3.57)	1.83 (0.12; 3.55)	0.48 (-2.51; 3.46)	0.32 (-2.67; 3.32)	-1.15 (-0.30; 2.60)	0.94 (-0.53; 2.41)
SWM strategy (hits)	457								
Low		0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate		0.41 (0.02; 0.81)	0.47 (0.07; 0.88)	0.05 (-0.31; 0.42)	0.06 (-0.31; 0.42)	0.01 (-0.67; 0.70)	0.03 (-0.66; 0.72)	0.33 (-0.10; 0.75)	0.36 (-0.07; 0.80)
High		0.16 (-0.31; 0.64)	0.16 (-0.32; 0.64)	0.33 (-0.10; 0.78)	0.33 (-0.12; 0.77)	-0.22 (-1.00; 0.56)	-0.25 (-1.03; 0.53)	0.31 (-0.07; 0.69)	0.33 (-0.06; 0.71)

Adjusted = sex, age, area, head injury, smoke, alcohol, drugs, farm residence
**Adjusted+mobilephone ownership (binary)*
Adjusted 1 = Adjusted+mother employment, mother education, home language, household size, government grant, repeated grade
**Adjusted 1+mobilephone ownership (binary)*
Data presented as the Beta from linear regression models
Motor Screening (MS); Reaction Response (RR); Spatial Working Memory (SWM); Paired Associate Learning (PAL); Multi-tasking (MTT); Rapid Visual Information Processing (RVP)

In age-stratified models (See Supplementary, Tables 6&7) similar results were found for children and adolescents.

3.4 Discussion

In our cohort in rural Western Cape of South Africa, about one third of the adolescents regularly use a mobile phone and about a third of the cohort spend time in front of an e-media screen. About a half of mobile phone users report mobile phone related awakenings at least once a week which was associated with an increased risk for sleep disturbances and headache severity as well as lower HRQoL. Furthermore, our study suggests some beneficial effects from e-media use on cognitive performance in this cohort, after adjusting for several socio-demographic factors. Nevertheless, we also found indication that unmeasured confounding might be an alternative explanation for the observed associations.

The low prevalence of one third mobile phone and e-media users found in this cohort, may be explained by both the infrastructure and connectivity in the rural outskirts, as well as the low SES in these rural areas. Recent studies from the Western Cape found that only 12% of disadvantaged communities in rural areas had access to free WIFI and high school learners experience substantial difficulty accessing public spaces for this service. [58 60] Inconsistent connectivity and fear of device theft is further a barrier to accessing the public hot-spots as well as a lack of infrastructure and trained personal to troubleshoot and educate or empower the use of technology and internet use.

Within the SA context, inequality remains common, especially amongst the most disadvantaged group in the rural outskirts. Socio-economic status varies even amongst this rural cohort, although we see that the majority are on the lowest economic bracket. We found those who report to own a mobile phone and or use an electronic device are associated with increased HRQOL compared to those who do not. This is unlikely to be causal but rather suggest that mobile phone ownership is a proxy for a better lifestyle. Thus, it is a big challenge in such a heterogeneous setting to evaluate the effects of mobile phone and e-media use. A recent study criticized the lack of conceptualizing SES on a multi-dimensional level to include the context and children's development in health research.[76] They found that of the multi-dimensional factors they included to measure economic well-being on child development including areas of mental, physical health and executive functioning, material assets had the highest association with child health outcomes and fiscal capacity the lowest. We can relate this to our observed findings in the models adjusted for mobile phone, removing the association to economic well-being revealed a more accurate pattern of the health symptoms in this exposure group. It is most likely that the decline in health symptoms compared to non-users reflects residual confounding as outlined above. However, symptoms were more prevalent in the highest exposure group, compared to moderate users and non-users in this rural cohort. Sleep disturbance has been widely associated with e-media use. Several studies found an increased prevalence of sleep disturbance and headaches amongst those using e-media for at least 30 minutes a day, and those who texted late at night [77 78]. It is complex to determine the causal effects of sleep disturbance on cognitive performance amongst e-media users, but a study found that those who texted late at night, had worse academic performance [78].

Lower HRQoL and more prevalent headache and sleep disturbance, reflected in our findings, may be explained by the recent trends in rural settings that adolescents spend less time outside, which may result in lower physical fitness. There is evidence of high cyber-bullying amongst this age group, a global public health concern including SA and Cape

Town, impacting emotionally and academically [79 80 81].

Studies describe that the age and development stage is particularly important to consider for the developmental impact, learning gain or detrimental effects from e-media use.[82,83] A study on determinants to social media amongst SA rural youth reported positive associations to obligation, knowledge sharing and also a habit.[84] Several studies are also indicating that the mental state of children and adolescents who are anxious and depressed may depend on e-media to feel better, resulting in dependency.[61,66 ,85]

When interpreting the results of this study one should also take into account differences in the way e-media is used in LMIC compared to Europe or the US. It has been proposed that young people in LMIC access Facebook and social media mainly for education and social support rather than for entertainment. [86 87] All these aspects may explain why our findings differ to some extent from e-media studies in Europe and Northern America. In developed countries, mainly negative associations between HRQoL and e-media use are observed in children and adolescents. [65 66 63] In our study associations tended to be less pronounced and we also observed beneficial associations. In particular, cognitive functions tended to be improved in our e-media users in line with, recent evidence of cognitive improvement in working memory amongst e-media users [88]. Those who played an educational application on a tablet expressed improved working memory performance compared to those who watched TV. Using e-media includes many cognitive tasks across the domains including multitasking, depending on the activity and level of engagement. Connection to the internet can be both an educational, empowering, knowledge based source, as well as a social connectivity tool, especially for this population of adolescence who are developmentally in an interpersonal phase of growth.[62,89,82]
However, it was also hypothesized that a high dose of radiofrequency electromagnetic fields (RF-EMF) of the brain from using e-media may impair cognitive function. In a recent cohort study of Swiss adolescent's cumulative RF-EMF dose of the brain found that a high dose of radiofrequency electromagnetic fields of the brain was associated with poorer memory but not with unspecific symptoms such as headache and sleep disturbances.[90] This may further be investigated in rural cohorts as EMF emissions are expected to be higher in areas with lower connectivity.[90]
In contrast to studies from Europe and North America, we see the lowest number of unspecific symptoms for moderate e-users. Our medium users were actually low e-media users in comparison to developed countries and this may explain the different findings to those settings, where moderate use implies longer duration. In our rural setting moderate e-media users, seem to benefit from the social and educational aspects.
Our study suggests that the amount of e-media use is very critical in relation to health. Extensive use seems to compensate for the beneficial effects of communication as it may involve misuse and behavioral dependency of e-media.[73]

Since the problems amongst adolescents with dependency and sleep are a growing concern, pediatricians have developed and validated screening tools to support parents to identify problematic e-media behaviors in adolescence.[91,92]

Strengths and limitations

These results are novel in its comparison of various aspects of e-media use in three different areas from rural South African setting. We collected extensive data about e-media use and health during school visits resulting in complete participation and absence of selection bias. A further strength is the objective of electronic cognitive assessments using a validated test battery and standardized software.

The cross-sectional approach is a limitation and longitudinal analyses are required to exclude reverse causality. For instance, we cannot exclude that lack of sleep influences the use of e-media. We have seen that adjusting for mobile phone ownership had strong effects on some of the risk estimates. Mobile phone ownership may thus represent unmeasured confounding such as educational style, parenting style, socio-economic context, and personality type

3.5 Conclusion

On the one hand, our findings contribute to the existing body of knowledge regarding health implications of problematic aspects of e-media use, showing similar associations for extensive e-media use as in high-income countries despite a considerably lower prevalence of such problematic aspects. On the other hand, we could also identify benefits from e-media use, in particular for the cognitive performance of moderate users. We thus recommend for low and middle income countries that the educational benefit of e-media device use in children and adolescents are implemented with caution of the potential negative side effects from problematic aspects of e-media use.

Contributors

MR and SM were involved with the conceptualization and formal statistical analysis of the paper. AD and MR are the principal investigators. SM is responsible for the original draft and together with MR the editing and development of versions thereafter. -. AD, WB, SM, and SF were responsible for the project administration of the study. All authors, including ME and SH, reviewed the final versions.

Declaration of interests

The authors declare that they have no competing interests in this study.

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3.6 Supplementary Material

Different aspects of electronic media use, symptoms and neurocognitive outcomes of children and adolescents in the rural Western Cape region of South Africa

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Exposure Variables	Question/s and tools	Choice Scale	Variable Type	Tool description
1.Duration of calls	"How long do you call with a mobile phone on average per day (incoming and outgoing calls)?"	Average minutes per day	Categorical	Survey
2. Total screen time	1. "If you are on the internet with the phone, what are you doing and for how long each day on average?" 1.1 Watching videos 1.2 reading news and other internet sites 1.3 being active on social media (eg: Facebook, Snapchat, Instagram, Musicaly) 1.4 Playing online games 2. "Do you use a computer / laptop / tablet PC (e.g. iPad)? If so, for how long?" 3. How many text messages (including WhatsApp-, Facebook, iMessage, Snapchat, Instagram, Musicaly etc) do you send on average from a mobile phone?	Average minutes per day	Categorical	Survey
3. Night-time mobile phone awakenings	"Are you sometimes woken up in the night by a message or call on your mobile phone or on another mobile phone in your sleeping room?"	No. of times per week	Categorical	Survey
4. Problematic mobile phone use	Mobile Phone Problem Use Scale - 10 (MPPUS-10) 10 items on behavioral addictions from questions relating to the categories of 'withdrawal', 'loss of control', 'negative life consequences' and 'craving'	Not true at all to extremely true	Items summed to create a continuous variable representing a total score, the higher the score, the higher the indication for dependency on mobile phone use	This tool has been validated across cultures including the HERMES (Health Effects Related to Mobile phone usE in adolescentS) cohort study.[73]
Health Outcomes				
1. Sleep disturbance	Four standardized questions on sleep disturbance: difficulties with falling asleep, restless sleep, involuntary awakenings and too early morning awakenings	Likert scale: never, rarely, sometimes and always, coded from 0 to three	The total score, continuous variable, ranges from a minimum of 0 and maximum of 12	Swiss Health Survey[93]

2. Health Related Quality of Life (HRQoL)	KIDSCREEN-10 questionnaire on wellbeing in the areas of physical, psychological, relational support and school environment	Five point likert scale	Two negative factor variables from the KIDSCREEN survey namely, sad and lonely, were converted to positive variables. Ordinal categorical data was then summed to create a continuous total score for HRQOL which was converted to a T-value using the Rasch parameter estimate code	KIDSCREEN-10 Handbook guidelines[94, 95]
3. Headaches	Headache Impact Test (HIT-6) for the severity of headaches with questions on tiredness, concentration and exhaustibility	Five point likert scale	Total score was obtained by summing up the score from all questions resulting in a score ranging from 36 to 78	HIT-6 guidelines[96, 97]
4. Cognitive performance	Cambridge Automated Neuropsychological Test Battery (CANTAB); three cognitive domains: a. processing speed, b. attention and c. memory	Two CANTAB tests per domain which measures cognitive performance by recording several performance scores, including latency and accuracy for each task within each test	Continuous data scores from the CANTAB were transformed to the closest normal distribution. The latency scores in milliseconds per task were inversed to a speed measure. Inaccuracy scores were converted to accuracy scores for consistent result presentation and dichotomized into binary variables (yes/no) for analysis. Outliers were excluded if any value was 3·25 standard deviations above and below the mean	a. Processing speed, test one, *motor screening (MS)*, and test two, *reaction time (RT)*, determines the processing ability to perform a mental task by screening sensorimotor and comprehension abilities, including an assessment of their ability to complete the test battery. b. Attention is assessed via test one, *rapid visual information processing (RVIP)*, based on sustained attention, requiring three cognitive functions: the ability to hold a target sequence in mind; constantly apply this figure to a stream of numbers presented; and lastly to calculate if the previous three figures match this sequence; and test two, assesses executive functioning via a *multi-tasking test (MTT)*, using simultaneous arrows and direction to measure cued attention set-shifting. c. Memory, *Paired Associates Learning(PAL)*, tests visual memory and new learning ability which are both measures for episodic memory, while test two, *spatial working memory (SWM)*, tests further skills of manipulating visual information and strategy use *(third test: spatial working memory (SWM)strategy test)*, measurements of executive functioning.[74]

Table 1: Description of all four exposure and health outcome tools used in the analysis

Table 2: Demographic comparison of the cognitive performance variables in relation to sex and grade

Neurocognitive Outcomes	Mean (SD)	Sex (F) Mean (SD)	Sex (M) Mean (SD)	Grade (1-2) Mean (SD)	Grade (4-6) Mean (SD)	Grade (7-9) Mean (SD)	Min-Max
PROCESSING SPEED							
1. Motor Screen Speed	*1.12 (0.4)	1.15 (0.40)	1.07 (0.39)	1.04 (0.40)	1.13 (0.39)	1.16 (0.40)	0.27-2.11
2. Motor Screen Accuracy (hits)	9.88 (0.84)	9.88 (0.82)	9.88 (0.86)	9.51 (1.66)	9.94 (0.58)	9.97 (0.24)	0-10
3. Reaction Time Speed	*4.35 (1.18)	4.18 (1.1)	4.53 (1.04)	4.17 (1.07)	4.43 (1.08)	4.16 (4.16)	0.53-9.09
4. Reaction Time Accuracy (hits)	24.87 (7.28)	24.94 (7.79)	24.78 (6.68)	23.60 (7.88)	25.08 (7.02)	25.25 (7.63)	0-30
ATTENTION							
5. Rapid visual info processing speed	*2.39 (0.73)	2.34 (0.69)	2.43 (0.76)	2.37 (0.87)	2.35 (0.68)	2.52 (0.75)	0.57-5.29
6. Rapid visual info processing accuracy (hits)	0.81 (0.11)	0.83 (0.11)	0.81 (0.11)	0.76 (0.12)	0.83 (0.11)	0.85 (0.10)	0.41-0.99
7. Multi-tasking speed	*1.33 (0.26)	1.31 (0.25)	1.35 (.27)	1.25 (0.33)	1.32 (0.25)	1.41 (.23)	0.72-4.20
8. Multi-tasking accuracy (hits)	120.80 (19.33)	119.85 (18.84)	121.87 (19.83)	114.75 (16.74)	120.04 (19.28)	129.46 (19)	54 -158
MEMORY							
9. Paired associates learning accuracy (hits)	11.62 (4.21)	11.65 (4.04)	11.59 (4.37)	10.15 (4.77)	11.84 (4.06)	12.18 (3.91)	0-20
10. Spatial working memory accuracy (hits)	18.80 (5.44)	18.64 (5.27)	18.97 (5.62)	17.86 (5.24)	18.60 (5.28)	20.43 (5.87)	0 -41
Total (n)	1001	526	471	161	665	171	

hit -the number of correct hits
**the latency in seconds per task was inversed to a speed measure*

Table 3: CANTAB outcome variable analysis – the number of participants categorized as missing and or outlier

	No. of participants	No. Missings	No. Outliers (3.25 SD above or below the mean)	Resolved
EXPOSURES				
Geronimo	0			
MPPUS-10	5	1 out of 10 items		Item imputation
OUTCOMES				
Hit6	2	all 6 items		Omitted from analysis
HRQOL	4	1 out of 5 items		Item imputation
Sleep Disturbance	3	all 4 items		Added to none category
CANTAB				
Processing Speed				
Motor screening	16	5	11 (<3.25)	Removed from analysis
Reaction Time	40	2	38 (>3.35)	Removed from analysis
Attention				
RVIP Processing	20	17	3 (<3.25)	Removed from analysis
Multi-tasking	15	6	9 (>3.25)	Removed from analysis
Memory				
PAL	29	3	26 (<3.25)	Removed from analysis
Spatial Working Memory	10	3	3 (2>3.25; 1<3.25)	Removed from analysis

Table 4: The distribution of the exposure variables by sex in the study sample

Behavior Category	Categorical Variable	Full sample Frequency (%)	Subsample with demographics Frequency (%)	Male (%)	Female (%)	Gender difference Chi^2 P-value
		Total (N=1001)	Sub-Total (n=482)	Male (%) (n=473)	Female (%) (n=528)	
Low	Duration calls per day					*0.39*
Medium	0	726 (72)	369 (77)	341(72)	385 (73)	
High	<=5 mins a day	185 (19)	72 (15)	94 (20)	91 (17)	
	>6 mins a day	90 (9)	41 (9)	38 (8)	52 (10)	
	Total screen time					
Low	0	540 (54)	284 (59)	268 (57)	308 (58)	*0.32*
Medium	Average minutes per day≤55	248 (25)	108 (22)	103 (22)	109 (21)	
High	Average minutes per day>55	213 (21)	90(19)	102 (22)	111 (21)	
	Awakenings					
Low	0	927 (93)	442 (92)	438 (93)	489 (93)	*0.99*
Medium	Average times per week<1.5	30 (3)	21 (4)	14 (3)	16 (3)	
High	Average times per week≥1.5	44 (4)	19 (4)	21 (4)	23 (4)	
	MPPUS-10					
Low	0	683 (68)	350 (73)	318 (67)	365 (69)	*0.59*
Medium	Score category:10-35	159 (16)	57 (12)	81 (17)	78 (15)	
High	Score category:36-91	159 (16)	75 (16)	74 (16)	85 (16)	
	Total N (%)	1001 (100)	482 (100)	473 (47)	528 (53)	

Table 5: Cognitive domains and tests performed within the CANTAB cognitive assessment battery

	Cognitive domain	Test	Cognitive function	Outcome	Duration of test
1	Processing speed including visual motor integration	Reaction Response (RR)	Perception of visual stimuli, response to visual stimuli and execution of motor action	movement time, reaction time and response accuracy;	6 minutes
		Motor Screening (MS)	Sensorimotor or perceptual motor speed and comprehension difficulties	Time lapse between display to response; number of correct and incorrect responses	2 minutes
2	Memory including executive Functioning	Spatial Working Memory (SWM)	Manipulation of visuo-spatial information, executive demands of strategy (reasoning, decision making and behaviour), parts of short-term memory (holding) concerned with immediate conscious perceptual and linguistic processing	Visits, re-visits and searches for boxes	5 minutes
		Paired Associate Learning (PAL)	Visual memory and new learning, episodic memory (collection of past, personal experience that occurred at a particular time and place with associated emotions)	Incorrect selection, adjustment, problem solving and memory of selection	8 minutes
3	Attention	Multi-tasking (MTT)	Attentional set-shifting, cognitive flexibility and lateralization	Congruency and latency during change of instructions	8 minutes
		Rapid Visual Information Processing (RVP)	Sustained attention and continuous performance, impulse control or inhibition	Sensitivity to target and correct responses	7 minutes

Symptoms	Duration of calls [95%CI]		Screen Time [95%CI]		Mobile phone related awakenings [95%CI]		Mobile phone Problematic use [95%CI]	
	Age 9-11 (n=592) Adjusted	Age 12-16 (n=406) Adjusted	Age 9-11 (n=592) Adjusted*	Age 12-16 (n=406) Adjusted*	Age 9-11 (n=592) Adjusted*	Age 12-16 (n=406) Adjusted*	Age 9-11 (n=592) Adjusted	Age 12-16 (n=406) Adjusted
Sleep disturbance								
Low	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Medium	-1.20 (-1.85; -0.54)	-1.28(-1.99; -0.56)	0.08 (-0.55; 0.71)	-1.07 (-1.87; -0.28)	0.67 (-0.84; 2.18)	-0.09 (-0.72; 1.35)	-2.00 (-2.69; -1.31)	-1.80 (-2.60; -1.00)
High	1.09 (0.25; 2.93)	0.51 (-0.42; 1.44)	0.38 (-0.26; 1.02)	0.06 (-0.75; 0.87)	1.51 (0.25; 2.76)	2.51 (1.25; 3.77)	0.65 (-0.01; 1.32)	0.18 (-0.54; 0.89)
HRQoL								
Low	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Medium	6.61 (4.16; 9.05)	4.84 (2.34; 7.34)	1.50 (-0.80; 3.80)	0.89 (-1.80; 3.58)	-1.79 (-7.36; 3.78)	3.04 (-1.87; 7.94)	8.35 (5.77; 10.92)	8.60 (5.88; 11.31)
High	3.24 (0.11; 6.37)	2.24 (-0.94; 5.43)	-0.76 (-3.10; 1.59)	0.17 (-2.61; 2.94)	-1.25 (-5.87; 3.37)	-5.38 (-9.62; -1.15)	2.27 (-0.22; 4.76)	2.56 (0.15; 4.98)
Headaches								
Low	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Medium	-6.95 (-9.00; -4.89)	-6.52 (-8.87;-4.17)	-0.43 (-2.38; 1.52)	-2.99 (-5.57; -0.41)	1.92 (-2.76; 6.60)	3.98 (-0.80; 8.77)	-9.42 (-11.56; -7.28)	-10.73 (-13.22; -8.24)
High	0.16 (-2.50; 2.82)	0.69 (-2.30; 3.69)	1.95 (-0.03; 3.94)	0.34 (-2.34; 3.01)	7.10(3.21; 10.98)	2.80 (-1.33; 6.93)	-0.96 (-3.04; 1.12)	0.70 (-1.51; 2.92)

Table 6: Linear regression analysis results - change in health score for participants belonging to the medium or high exposure group with respect to e-media use, duration of mobile phone calls and screen time, stratified by age groups. Significant estimates (p<0.05) in bold.

Adjusted = sex, age, area, head injury, smoke, alcohol, drugs, farm residence
**Adjusted+mobilephone ownership (binary)*

Table 7: Linear regression analysis results - change in cognitive performance for participants belonging to the medium or high exposure group with respect to e-media use, duration of mobile phone calls and screen time stratified by age groups. Significant estimates (p<0.05) in bold. Refer to Table 5 above, for test name and description in each domain.

Neurocognitive Outcomes	Duration of calls		Screen Time		Mobile phone related awakenings		Mobile phone Problematic use	
	Age 9-11 (95%CI) Adjusted	Age 12-16 (95%CI) Adjusted	Age 9-11 (95%CI) Adjusted*	Age 12-16 (95%CI) Adjusted*	Age 9-11 (95%CI) Adjusted*	Age 12-16 (95%CI) Adjusted*	Age 9-11 (95%CI) Adjusted	Age 12-16 (95%CI) Adjusted
PROCESSING SPEED								
MS Speed	n=588	n=409	n=588	n=409	n=588	n=409	n=588	n=409
Low	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate	0.01 (-0.09; 0.10)	-0.01 (-0.12; 0.10)	0.03 (-0.06; 0.12)	0.11 (-0.01; 0.23)	-0.09 (-0.31; 0.12)	0.23 (0.01; 0.45)	0.05 (-0.06; 0.15)	-0.06 (-0.19; 0.06)
High	0.03 (-0.09; 0.15)	-0.08 (-0.22; 0.06)	-0.01 (-0.10; 0.08)	0.13 (0.00; 0.25)	0.04 (-0.14; 0.21)	-0.04(-0.23; 0.15)	0.04(-0.06; 0.14)	0.01(-0.10; 0.12)
RR Speed	n=573	n=388	n=573	n=388	n=573	n=388	n=573	n=388
Low	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate	0.10 (-0.16;0.32)	0.12 (-0.17; 0.41)	0.11 (-0.12; 0.33)	0.40 (0.08; 0.71)	0.47 (-0.08; 1.01)	0.20 (-0.38; 0.77)	0.00 (-0.25; 0.26)	-0.08 (-0.41; 0.25)
High	0.11 (-0.20; 0.42)	0.25 (-0.22; 0.53)	0.16 (-0.07; 0.39)	0.45 (0.12; 0.77)	0.28 (-0.18; 0.73)	0.56 (0.05; 1.06)	0.11 (-0.14; 0.36)	0.10 (-0.19; 0.39)
ATTENTION								
RVP speed	n=576	n=405	n=576	n=405	n=576	n=405	n=576	n=405
Low	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate	-0.02 (-0.19; 0.16)	0.16 (-0.03; 0.35)	0.25 (0.09; 0.41)	-0.02 (-0.22; 0.19)	-0.18 (-0.57; 0.22)	0.34 (-0.04; 0.72)	0.12 (-0.06; 0.31)	0.16 (-0.05; 0.38)
High	-0.12 (-0.34; 0.11)	0.17 (-0.07; 0.41)	0.02 (-0.14; 0.18)	0.27 (0.05; 0.48)	0.03 (-0.31; 0.36)	-0.25 (-0.58; 0.07)	-0.10 (-0.28; 0.08)	0.19 (0.00; 0.38)
RVP accuracy (hits)	n=577		n=577	n=407	n=577	n=407	n=577	n=407
Low	0 (ref)	n=407	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate	-0.00 (-0.03; 0.02)	0 (ref)	0.01 (-0.02; 0.03)	0.02 (-0.01; 0.05)	0.02 (-0.04; 0.08)	0.02 (-0.04; 0.07)	-0.00 (-0.03; 0.02)	0.03 (-0.00; 0.06)
High	-0.12 (-0.05; 0.02)	0.02 (-0.01; 0.05)	-0.01 (-0.03; 0.02)	0.02 (-0.01; 0.05)	-0.01 (-0.05; 0.04)	-0.02 (-0.06; 0.03)	-0.01 (-0.04; 0.01)	0.00 (-0.02; 0.03)
		0.00 (-0.03; 0.04)						
MTT speed	n=581	n=405	n=581	n=405	n=581	n=405	n=581	n=405
Low	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate	-0.02 (-0.07; 0.03)	0.02 (-0.03; 0.08)	0.00 (-0.04; 0.05)	0.07 (0.01; 0.13)	-0.01 (-0.12; 0.10)	0.04 (-0.07; 0.02)	-0.02 (-0.07; 0.03)	0.03 (-0.03; 0.09)
High	0.07 (0.01; 0.13)	-0.01 (-0.08; 0.06)	0.01 (-0.04; 0.05)	-0.01 (-0.03; 0.11)	0.06 (-0.03; 0.15)	0.08 (-0.02; 0.17)	0.03 (-0.02; 0.08)	-0.00 (-0.06; 0.05)
MTT accuracy	n=585	n=409	n=585	n=409	n=585	n=409	n=585	n=409
Low	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)

Moderate	5.01 (0.64; 9.38)	4.65 (-0.51; 9.82)	0.95 (-3.15; 5.05)	-0.78 (-6.40; 4.83)	3.75 (-6.16; 13.65)	0.18 (-10.17; 10.53)	1.18 (-3.48; 5.85)	3.38 (-2.40; 9.17)
High	-1.32 (-6.93; 4.30)	1.33 (-5.25; 7.92)	3.52 (-0.67; 7.70)	-2.49 (-8.30; 3.31)	3.22 (-5.18; 11.61)	-4.94 (-13.87; 3.99)	4.32 (-0.19; 8.83)	2.89 (-2.25; 8.03)
<u>MEMORY</u>								
PAL accuracy (hits)	n=566	n=403	n=566	n=403	n=566	n=403	n=566	n=403
Low	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
Moderate	-0.08 (-0.00; 0.83)	0.69 (-0.35; 1.72)	-0.10 (-0.97; 0.76)	0.18 (-0.94; 1.29)	0.51 (-1.59; 2.60)	0.22 (-1.84; 2.29)	-0.37 (-1.33; 0.60)	0.26 (-0.89; 1.42)
High	-0.79 (-1.96; 0.38)	0.15 (-1.16; 1.47)	-0.33 (-0.54; 1.20)	-0.80 (-1.95; 0.35)	-1.69 (-3.44; 0.07)	0.55 (-1.26; 2.36)	-0.01 (-0.95; 0.93)	0.60 (-0.43; 1.63)
SWM accuracy (hits)								
Low	n=585	n=406	n=585	n=406	n=585	n=406	n=585	n=406
Moderate	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
High	0.17 (-1.08; 1.42)	1.45 (-0.04; 2.94)	0.65 (-0.52; 1.82)	0.22 (-1.40; 1.84)	2.12 (-0.69; 4.94)	2.2 (-0.72; 5.25)	0.11 (-1.21; 1.44)	-0.33 (-1.99; 1.33)
	-0.09 (-1.68; 1.50)	-0.24 (-2.14; 1.66)	0.39 (-0.80; 1.58)	0.65 (-1.02; 2.33)	-0.77 (-3.16; 1.61)	0.13 (-2.44; 2.71)	-0.07 (-1.35; 1.20)	1.56 (0.08; 3.04)
SWM strategy (hits)								
Low	n=583	n=408	n=583	n=408	n=583	n=408	n=583	n=408
Moderate	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
High	0.44 (0.10; 0.78)	0.21 (-0.17; 0.59)	0.25 (-0.07; 0.56)	-0.17 (-0.58; 0.24)	0.01 (-0.75; 0.78)	-0.05 (-0.81; 0.71)	0.34 (-0.02; 0.70)	0.04 (-0.38; 0.47)
	0.22 (-0.21; 0.65)	0.08 (-0.40; 0.57)	0.10 (-0.22; 0.42)	-0.05 (-0.48; 0.37)	-0.14 (-0.79; 0.50)	0.00 (-0.66; 0.65)	0.33 (-0.01; 0.68)	0.29 (-0.09; 0.66)

Adjusted = sex, age, area, head injury, smoke, alcohol, drugs, farm residence

*Adjusted +mobile phone ownership (binary)

Data presented as the Beta coefficients with confidence from linear regression models

Motor Screening (MS); Reaction Response (RR); Spatial Working Memory (SWM); Paired Associate Learning (PAL); Multi-tasking (MTT); Rapid Visual Information Processing (RVP)

Table 8: Socio-economic status variables stratified by area

Variable	Choice Categories	Frequency (%)	Area 1 (%)	Area 2 (%)	Area 3 (%)	Chi^2
		Total (N=482)	(n=105)	(n=139)	(n=238)	P-value
maternal employment	Unemployed/Other	175 (36.3)	51 (48.6)	71 (51.1)	53 (22.3)	<0.01
	Employed	307 (63.7)	54 (51.4)	68 (48.9)	185 (77.7)	
maternal education	<=primary	199 (41.3)	33 (33.3)	44 (31.7)	120 (50.4)	<0.01
	>=secondary	283 (58.7)	70 (66.7)	95 (68.4)	118 (49.6)	
home language	Afrikaans	317 (65.8)	98 (93.3)	139 (100)	80 (33.6)	<0.01
	Non-Afrikaans	165 (34.2)	7 (6.7)	0 (0)	158 (66.4)	
household size	2-4members	182 (37.8)	32 (30.5)	34 (24.5)	116 (48.7)	<0.01
	5-6members	183 (37.9)	35 (33.3)	55 (39.6)	93 (39.1)	
	7+ members	117 (24.3)	38 (36.2)	50 (36)	29 (12.2)	
government grant	childsupportgrant	329 (68.2)	53 (50.5)	90 (64.8)	186 (78.2)	<0.01
	other grant	105 (21.8)	35 (33.3)	39 (28.1)	31 (13.0)	
	no grant	48 (10)	17 (16.2)	10 (7.2)	21 (8.8)	

Chapter 4

4. Maternal alcohol exposure

Maternal smoking and drinking behavior during and after pregnancy in relation to neurocognitive function of school-children in the rural Western Cape

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4.1 Abstract

Background: Maternal substance use and its long-term effect on the neurocognitive functions of children is a global public health issue. Despite an increase in substance use in rural areas of low to middle income countries, research is limited in these populations.

Objective:

We have therefore explored the effect of maternal drinking and smoking behaviors on the neurocognitive functioning of rural school children.

Method: A cross-sectional analysis on the determinants of current, past and gestational maternal alcohol use and gestational smoking on child neurocognitive functions was conducted on school-children (N=482), imbedded within the child health agricultural cohort (CapSA) study across seven schools in rural Western Cape, South Africa. Standardised neurocognitive assessment tools included the Cambridge Automated Neuropsychological Battery (CANTAB) and the KIDSCREEN-10 to measure health related quality of life via a child questionnaire. Maternal Smoking and drinking behaviour was captured by means of a parent/guardian questionnaire.

Results: Of the 482 parents/guardians who completed the survey, 29% reported current drinking 27% reported past drinking and 10% reported maternal gestational drinking, while 31% reported gestational smoking. Significant associations were observed between past and current maternal drinking and child's reduced rapid visual processing accuracy in attention [Beta:-0.03; 95%-confidence interval: -0.05;-0.004] and between maternal drinking and reduced child's spatial working memory [-0.59; (-1.02; -0.15)]. Heavy (>5 cigarettes per day) gestational smoking was associated with lowered child's learning in memory [-1.69; (-3.05; -0.33)] and lower health related quality of life [-3.41;(-6.64; -0.17)]. The odds of child repeating a grade was 1.69 (2.81-1.02)] for those exposed to maternal gestational smoking and 1.68 (3.31-0.85)] for those exposed to maternal drinking compared to those who were not exposed.

Conclusion: The consistent negative associations across all four maternal substance use proxies, six neurocognitive health outcomes and one health symptom is suggestive of adverse health effects, warranting longitudinal follow-up. Health policies to eliminate gestational substance are recommended.

Keywords: maternal alcohol use; maternal smoking; substance use, child cognitive functioning; rural; environmental exposures; child health

4.2 Background

The World Health Organisation (WHO) estimates that harmful use of alcohol contributes to 5.1% of the global burden of disease in 2016, with the disadvantaged and vulnerable populations having higher rates of alcohol-related deaths and hospitalizations.[1] Heavy maternal alcohol during pregnancy is associated with the chronic life-long disability of Fetal Alcohol Syndrome Disorder (FASD), most prevalent amongst low socio-economic status in communities of both developed and developing countries. [2 3] FADS occurs on a spectrum with a range of features including facial dysmorphia, growth deficiency and neurobehavioral impairment present in full Fetal Alcohol Syndrome (FAS) to partial FAS (PFAS) and Alcohol-related Neurodevelopmental Disorders (ARND).[3 4] Hence, many children who may have the latter asymptomatic features or non-dysmorphic facial features, go undiagnosed until the long-term effects of maternal drinking on neurobehavioral functioning is typically featured by persistent struggles in the mainstream classroom. South Africa`s Western Cape Province has the highest rate of Fetal Alcohol Syndrome Disorder in the world, reporting 40.5-46.4 cases per 1000 births in 2000 to 68.0-89.2 per 1000 children in 2007, as compared to an average estimate of 0.97 per 1000 in developed countries.[5 6] More recent studies in SA estimate the total FASD to affect 182-259 per 1000 children or 18-26%, with FAS occurring in 93-128 per 1000 children, PFAS in 58-86, and, ARND in 32-46 per 1000. [2 4] A second study distinguished FAS (9-129 per 1000 children) and total FASD cases (196-276 per 1000 or 20-28%) in three rural communities in South Africa.[7] This struggle dates back to colonialism in the history of South Africans, where no labour laws existed during the apartheid regime, and farm labourers were frequently remunerated in alcohol rather than money, referred to as the Dop (Afrikaans translation for a drink) System. [8] This practice continued long enough to create dependency and the Dop legacy as it is referred to, even though the Dop System was declared illegal after apartheid ended in 1990. [9]

Very high rates of FASD exist in these rural areas and isolated towns where entrenched practices of regular binge drinking co-exist with challenging conditions for childbearing and child development. [4] Binge alcohol use has been clearly documented as the proximal maternal risk factor for FASD, and significant distal risk factors were: low body mass, education, and income; high gravidity, parity, and age at birth of the index child.[7] According to a recent study by Rochat and colleagues (2019) on the risk factors of maternal alcohol use in the Kwazulu Natal region of SA, food insecurity, parental mental health problems including stress and anxiety and child mental health problems were associated with double the odds of consuming alcohol. [10]

Results from a 2008-2010 survey in five farming communities in the Western Cape revealed that 83% of farmworkers were current drinkers compared to 65.5% of those who were not farm workers or in a different occupation; among current drinkers who consumed alcohol in the week preceding the interview, farmworkers consumed almost twice the amount of alcohol compared to others (15.2 *vs.*

8.9 drinks, $p = 0.008$); bingeing (five or more drinks per occasion for men; three or more drinks for women) is more prevalent among farmworkers than others (75.0% *vs.* 47.5% respectively, $p < 0.001$) and men were only slightly more likely to be current drinkers than women, 75.1% *vs.* 65.8% ($p = 0.033$), as females reported that they were under more stress than males. [9] Concurrently, London (2000) found that workers in the South Africa deciduous fruit industry with past experience of the Dop System were almost 10 times less likely to be abstainers from alcohol than colleagues without exposure to the Dop System. [11]

Within South Africa, there is limited research regarding the impacts of different forms of maternal alcohol consumption behaviours other than binging on child neurocognitive functioning (Katwan, 2010; Katwan et al., 2011; Rochat et al., 2019). Research has shown that there is a high rate of failure in the mainstream school system, particularly of rural schools and more so in the rural farming areas, while research on this topic of maternal consumption is limited to clinical settings in diagnosed patients rather than those undiagnosed presenting with the poor cognitive outcomes in school. [10]

Smoking is highly correlated with alcohol consumption.[5] Both gestational substance use behaviours are associated with cognitive impairment in children, through its hypotoxic effect on the development of the fetal brain. Yet this topic too has revealed inconsistent findings for similar reasons to research which explores the impact of maternal alcohol consumption on child cognitive outcomes. A review on long-term effects of maternal smoking during pregnancy on cognitive development has confirmed from several observational studies between 2000-2011, that there is a relationship between tobacco smoking exposure in utero and reduced academic achievement and cognitive abilities, independent of other factors. [12] This review concluded that that the majority of these studies were conducted in EU and U.S and research in other contexts are required to translate these results, yet most prevalent amongst low education and socio-economic status. [12] Furthermore, this review highlights importantly that mothers who do not smoke may be exposed to second hand smoke themselves, which is further associated to adverse health effects. [12]

The overarching aim of the current research study was to examine the relative impacts of potentially neurotoxic maternal substance use behaviors including current, gestational and past maternal alcohol use, and gestational smoking ondevelopmentally sensitive areas of child cognitive functioning and health related quality of life in undiagnosed mainstream school-going populations.

We hypothesized that children of mothers who reported participating in these drinking and smoking behaviours would perform worse across all the health outcomes, compared to children of mothers who did not report participating in these substance use behaviours (Adnams et al., 2001; Katwan, 2010; Katwan et al., 2011; Rochat et al., 2019).

4.3 Methods

4.3.1 Participants

The current study is embedded within the overarching Child health project in South Africa (CapSA) longitudinal cohort study, carried out between 2017 and 2019, which endeavoured to investigate the impacts of exposure to pesticides on child reproductive and neurocognitive outcomes within three agriculturally intensive areas of the Western Cape, namely: De Doorns, Grabouw and Piketberg (Chetty-Mhlanga et al., 2018). The current study and the overarching study have both previously received ethical approval from the University of Cape Town's (UCT's) Human Research Ethics Committee (HREC) (current study reference: 645/2018 [see Appendix A], CapSA reference: 234/2009).

The CapSA study protocol has been described elsewhere (Chetty-Mhlanga et al., 2018). To give a brief overview, a purposive sampling strategy was employed to recruit a sample of N=1001 children between the ages of 9 to 16 years from both town and farm schools within the three agriculturally intensive areas of interest in 2017 (Chetty-Mhlanga et al., 2018). Child participants were enrolled in equal numbers with regards to the three study areas, gender, and farm or non-farm residence (Chetty-Mhlanga et al., 2018). Moreover, mothers or guardians of the child participants were interviewed to obtain further information regarding child exposures and pertinent socio-demographic details. This study analysis matched data on 482 participants whose parent or guardian completed the socio-demographic and lifestyle survey.

4.3.2 Exposure and outcome measures

<u>Outcome Assessment</u>. The primary outcome measure for the current study was the *Cambridge Automated Neuropsychological Battery (CANTAB)*, used to assess different aspects of child cognitive abilities. Developed by a team of neuroscientists at Cambridge Cognition, the CANTAB is a flexible online neuropsychological assessment battery which provides the choice of an array of subtests which tap into different cognitive domains. [13 14 15 16]

Previous research has shown that the CANTAB is especially sensitive to variations in child neurocognitive functioning due to adverse exposures, such as maternal gestational alcohol use (Green et al., 2009; Mattson et al., 2010). Further research, including our study has also shown that the CANTAB can detect subtle changes in child cognitive functions in relation to different exposures such as pesticide related behaviour, e-media use and ??(Goldberg et al., 2005; Roque et al., 2011) and animal studies. [13 17 18]

The CANTABtest assess three cognitive *domains* as follows: (1) *processing speed* assessed by the motor screening test (MOT) and the reaction time task (RTI), (2) *attention* assessed by the rapid visual information processing task (RVP) and the multi-tasking test (MTT), and (3) *memory* assessed by the spatial working memory task (SWM) and the paired associates learning (PAL) (see supplement Table

A for details). Each cognitive function was measured in accuracy per task (the number of correct hits) and in latency (milliseconds) per task.

Health related quality of life (HRQol)

HRQoL was measured using the KIDSCREEN-10 questionnaire with a five point Likert scale on wellbeing in the areas of physical, psychological, relational support and school environment, then summed as a continuous total score.[19 13 20]

Overall Intelligence

A proxy for overall intelligence was used by the binary question in the guardian survey: "Did your child repeat any grades during primary school?".

<u>Smoking, drinking and covariate data</u>. Data regarding the exposures of interest on maternal substance use and related socio-demographic factors, were collected via the use of the guardian questionnaire on: (1) *general information section,* home language, household size and parental marital status and (2) the maternal specific *socio-demographic factors* of interest: maternal education and maternal employment. Participant questionnaires were used to collect information on the (1) child-specific socio-demographic factors of interest: child age and child sex and (2) lifestyle factors: electronic media use, head injury, farm residence or not, and substance use (smoking, drugs, alcohol use).

The latter section of the guardian questionnaire included questions regarding maternal alcohol use current, past and maternal drinking which were adapted from prior research studies conducted in South Africa regarding maternal alcohol consumption behaviours (Katwan et al., 2011; May et al., 2005; May et al., 2008; Viljoen, Croxford, Gossage, Kodituwakku, & May 2002) (see Table 1). These questions were initially framed in terms of drinking frequency, providing several response options for the respondents to consider (i.e. [0] Never, [1] <1 glass a day, [2] ≈1 glass a day [3] >1 glass a day). Gestational smoking was further enquired "did the mother smoke during pregnancy" providing the five response frequencies "[1] Never , [2] Less than one cigarette a day, [3] 1-5 cigarettes a day, [4] 5-20 cigarettes a day, [5] More than a packet a day. Household smoking was enquired as: "does anyone in the household currently smoke or ever smoked at home?" with responses quantified according to the number of people in the house who smoke: "[1] None , [2] One, [3] Two, [4] More than two. Previous research has shown that when asking questions regarding socially sensitive topics, such as alcohol consumption, it is advisable to ask these questions towards the end of an interview once rapport has been established (Katwan et al., 2011; May et al., 2005; May et al., 2008). As such, in the current study, questions relating to maternal substance use were purposefully placed near the end of the interview to reduce response bias related to other varialbes.

4.3.2 Procedures

After having obtained consent from child and parents for study participation, children's cognitive functions were assessed at their schools, after appropriate logistical arrangements were made with the school administrative bodies, regarding appropriate dates and times for testing on school premises. Child data were collected at five separate stations with an allocated station for child neurocognitive testing. Trained fieldworkers carried out the neurocognitive testing at this station using iPads to administer the CANTAB. The CANTAB battery (see supplementary Tables S1 for test battery overview) was administered in groups of five to seven children at a time, in their preferred language (Afrikaans, isiXhosa or English), for an offline testing session lasting 40 minutes.

Data on maternal alcohol use behaviours and related socio-demographic factors were collected from mothers or guardians via the use of the Guardian Questionnaire. The Guardian Questionnaire was administered by trained fieldworkers to mothers or guardians at their place of residence at a time which suited the respondents. Data from these structured interviews were collected via online forms through the Open Data Kit (ODK) application which was pre-installed on the fieldworkers' mobile phones. The structured interviews with mothers or guardians lasted approximately one hour.

4.3.4 Analysis

The current study was cross-sectional of the baseline data collected in 2017 from asample of 482 children whose guardian were available for an interview.

For the analysis only CANTAB score data were used within ±3.5 standard deviations from mean score ((see Supplementary Table S2 and S3 for all participants). Maternal alcohol variables were dichotomised into binary predictors (never vs. ever) for the different maternal alcohol use behaviours since the relative frequencies of individuals in each drinking 'frequency' category were low (e.g. for the 9.8% of mothers who reported having participated in gestational alcohol use, 4.2% reported consuming <1 glass per day, 3.5% reported consuming = 1 glass/day, and 2.2% reported that they consumed > 1 glass/day). In addition, all exposure variables were categorised to observe any exposure response pattern.

Multiple linear and logistic regression were conducted. Factors that were considered relevant to adjust for potential variance in cognitive performance amongst children related to four categories: (i) *child-specific demographic factors* - age, sex, grade, area of residence, farm or non-farm residence (ii) *child development and lifestyle factors* - substance use, head injury and electronic media use (iii) *child development and education* - repeated a grade, attended preschool or not, received learner support or not (iv) *socio-economic status including general socio-demographic variables* -home language, household size, maternal education, maternal employment, government grant (v) *maternal lifestyle factors* maternal smoking, household smoking.

Altogether, 30 MR models were run (see Table 2) with each of the six CANTAB subtest outcomes. Final selection of confounding variables was based on step-wise regression analysis procedure to determine the most relevant confounders,which included those on a priori basis and informed by recent studies. A sensitivity analysis on the adjustment of socio-economic status as well as stratified analysis by sex, age groups and area were conducted, household smoking and pesticide use (behavioural exposure-related proxies, *eating* and *picking* fruit from the vineyard, orchard or nearby field)[21].

Statistical analyses for the current study was completed using Stata 16.0 verison.

4.4 Results

Table 1: Demographics of the children from the Western Cape, South Africa in this study and four maternal substance use behaviors.

**TBI –Traumatic Brain Injury*	**Total n (%)**	**Maternal Current drinking n (%)**	**P-value Chi²**	**Maternal Past drinking n (%)**	**P-value Chi²**	**Maternal Maternal drinking n (%)**	**P-value Chi²**	**Maternal gestational smoking n (%)**	**P-value Chi²**
TOTAL n (%)	**482 (100)**	**141 (29)**		**130 (27)**		**48 (10)**		**151 (31)**	
Age categories			**0.02**		**0.02**		0.35		0.06
9-11 years	284 (59)	92 (65)		90 (69)		29 (60)		97 (64)	
12-14 years	164 (34)	46 (33)		35 (27)		18 (38)		49 (32)	
15-16 years	34 (7)	3 (2)		5 (4)		1 (2)		5 (3)	
Grade categories			0.11		0.06		0.89		**<0.00**
2nd-3rd	79 (16)	26 (18)		24 (19)		8 (17)		29 (19)	
4th-6th	310 (64)	96 (68)		90 (69)		32 (66)		106 (23)	
7th-9th	93 (20)	19 (14)		16 (12)		8 (17)		16 (11)	
Sex			0.14		0.64		0.76		0.21
Male	251 (52)	66 (47)		70 (54)		24 (50)		85 (56)	
Female	231 (48)	75 (53)		60 (46)		24 (50)		66 (44)	
Area			**<0.00**		**<0.00**		0.92		**<0.00**
DeDoorns	105 (22)	44 (31)		39 (30)		10 (21)		45 (30)	
Piketberg	139 (29)	58 (41)		49 (38)		13 (27)		76 (50)	
Grabouw	238 (49)	39 (28)		42 (32)		25 (55)		30 (20)	
Child Head Injury (ever)			0.12		0.13		0.77		0.13
0 (none)	304 (63)	81 (57)		73 (56)		28 (58)		88 (58)	
1 (fell & hit head)	116 (24)	36 (26)		39 (30)		13 (27)		37 (25)	
2 (potential TBI*)	62 (13)	24 (17)		18 (14)		7 (15)		26 (17)	
Child Smoke(ever)			0.10		0.33		0.18		**0.02**
No	410 (85)	114 (81)		114 (88)		44 (92)		129 (79)	
Yes	72 (15)	27 (19)		16 (12)		4 (8)		31 (21)	
Child Alcohol Use (ever)			0.36		0.15		0.51		0.57
No	395 (82)	112 (79)		112 (86)		41 (85)		126 (83)	
Yes	87 (18)	29 (21)		18 (14)		7 (15)		25 (17)	
Child Drug Use (ever)			0.26		0.28		0.72		0.13
No	468 (97)	135 (96)		128 (98)		47 (98)		144 (95)	
Yes	14 (3)	6 (4)		2 (2)		1 (2)		7 (5)	
Mobile-phone use (ever)			0.32		0.14		0.28		0.42
No	303 (63)	98 (70)		88 (68)		38 (79)		106 (70)	
Yes	179 (37)	43 (30)		42 (32)		10 (21)		45 (30)	
Farm residence			**0.05**		**0.02**		0.78		0.07
No	468 (97)	79 (56)		71 (23)		31 (10)		86 (28)	
Yes	14 (3)	62 (44)		59 (33)		17 (10)		65 (36)	

Household smoking			**<0.00**		**<0.00**		0.11		**<0.00**
No	263(55)	50 (35)		49 (38)		21 (44)		38 (25)	
Yes	219 (45)	91 (65)		81 (62)		27 (56)		113 (75)	

Of the 482 parents/guardians who completed the survey, 29% reported current drinking 27% reported past drinking and 10% reported maternal drinking, while more than 50% in each group report gestational smoking (in total: 31%). Participating children were between 9-16 years old and 48% were female. Table 1 demonstrates that smoking and drinking behaviour is correlated with various demographic factors such as age of the children, area of residence, farm residence, whether a child smokes and whether there is report of household smoking. Interestingly, 21% of mothers who report gestational smoking, have children who report smoking compared to 15% of mothers who do not smoke (p=0.02).

Prior to the final model presented in Table 2 and 3, a sensitivity analysis was conducted (See supplementary S5) to compare a basic model with a model adjusted for socio-economic variables. Very small to no differences were observed between the two models, and significant findings remained the same. Since we observe some confounding by SES, the full adjusted model including socio-economic status variables was selected for the final model. Most importantly, the additional covariates did not change the power to observe the significant associations observed in this relation between maternal substance use and cognitive performance.

Supplementary Table S6, highlights the importance of variation by sex in the health effects we observe from maternal alcohol use. Although there is an inconsistent pattern observed, we observe the change in significance from the non-stratified analyses on rapid visual processing and both current and past maternal drinking, as the groups become smaller. Most importantly males rather than females are significantly affected by maternal drinking in memory (-0.68; [-1.30; -0.06]).

Table S7 on age group sensitivity analysis provides more details on age differences in our results. No specific pattern is observed across the results, yet quite clearly distinguishing that the younger age group rather than the older age group is significantly affected, in both HRQol (-6.04, [-10.05; -2.03]) and Spatial Working Memory (-0.67 [-1.22; -0.12]) in relation to maternal drinking and furthermore in HRQol (-3.15, [-5.88; -0.41]) in relation to maternal current drinking.

Table 2: Linear regression analysis results – associations of three maternal drinking exposures (Yes/No) with six cognitive performance outcome scores. Beta refers to a difference in scores between exposed and unexposed study participants.

			Current drinking (n=141)			**Past drinking (n=130)**			**Maternal drinking (n=48)**		
	Score	N	Beta (β)	95% CI	P-value	Beta (β)	95% CI	P-value	Beta (β)	95% CI	P-value
Health Related Quality of Life		482	-1.51	-3.54; 0.52	0.15	1.77	-0.28; 3.81	0.09	-2.74	-5.74; 0.26	0.07
Processing Speed											
Motor Screening	Speed (seconds)	482	-0.04	-0.12; 0.04	0.36	-0.02	-0.11; 0.06	0.58	-0.01	-0.14; 0.11	0.86
Reaction Response	Speed	458	-0.10	-0.32; 0.13	0.41	0.07	-0.16; 0.30	0.54	-0.19	-0.52; 0.15	0.27
Attention											
Rapid Visual Processing	Speed	472	-0.07	-0.23; 0.08	0.35	-0.01	-0.17; 0.14	0.88	0.04	-0.19; 0.26	0.76
	Accuracy (hits)	473	**-0.03**	**-0.05; -0.004**	**0.02**	**-0.03**	**-0.05; -0.004**	**0.02**	-0.01	-0.04; 0.03	0.65
Multi-tasking	Speed	474	-0.02	-0.06; 0.02	0.41	0.02	-0.02; 0.06	0.32	0.01	-0.05; 0.07	0.72
	Accuracy	477	-1.62	-5.68; 2.44	0.43	-0.16	-4.25; 3.93	0.94	-4.04	-10.00; 1.91	0.18
Memory											
Paired Associates Learning	Accuracy	462	-0.38	-1.22; 0.46	0.38	0.04	-0.81; 0.88	0.94	0.23	-1.04; 1.49	0.72
Spatial Working Memory	Accuracy	476	1.03	-0.12; 2.18	0.08	0.45	-0.72; 1.62	0.45	0.56	-1.13; 2.26	0.51
	Strategy	477	0.27	-0.26; 0.57	0.07	-0.04	-0.35; 0.26	0.77	**-0.59**	**-1.02; -0.15**	**0.01**

Adjusted for age, grade, sex, area, head injury, smoke, alcohol, drugs, farm residence, mobile phone problematic use score, mobile phone ownership, mother employment, mother education, home language, household size, government grant, repeated grade, preschool, learner support

In Table 2, HRQOL displays a non-significant negative trend with current and pregnancy related maternal drinking, reaching statistical significance in 9 to 11 year old children for drinking during pregnancy (Table S7). Most of the cognitive tests were negatively correlated with drinking and smoking but mostly non-significant except ,a significant decline in the performance of rapid visual processing accuracy [Beta (-0.03); CI (-0.05;-0.004)] for those whose mothers report current or past drinking. Further, a significant negative association betweene spatial working memory and maternal drinking during pregnancy was observed [-0.59; (-1.02; -0.15)]. Heavy maternal smoking during pregnancy (>5 cigarettes/day) was negatively associated with paired associates learning in memory [-1.73; (-3.10; -0.36)] and HRQOL [-3.41; (-6.64; -0.17)] (Table 3).

Table 3 The exposure response relationship between mothers who report gestational smoking less or more on child cognitive performance outcomes

	Gestational smoking							
	Ref- No smoking (n=331)		1-5 cigarettes/day (n=106)			>5 cigarettes/day (n=45)		
		n	Beta (β)	95% CI	P-value	Beta (β)	95% CI	P-value
Health Symptom.								
Health Related Quality of Life	Total	482	1.14	-1.19; 3.46	0.34	**-3.41**	**-6.64; -0.17**	**0.04**
Processing Speed								
Motor Screening	Speed	482	0.01	-0.09; 0.11	0.90	0.04	-0.10; 0.18	0.55
Reaction Response	speed	458	0.01	-0.25; 0.27	0.95	-0.19	-0.56; 0.18	0.31
Attention								
Rapid Visual Info Processing	Speed	472	0.01	-0.17; 0.18	0.95	-0.17	-0.42; 0.08	0.18
	accuracy	473	0.02	-0.01; 0.04	0.22	0.02	-0.02; 0.05	0.40
Multi-tasking	Speed	474	-0.01	-0.06; 0.04	0.72	-0.04	-0.11; 0.26	0.23
	accuracy	477	0.42	-4.26; 5.11	0.86	-0.52	-7.07; 6.04	0.88
Memory								
Paired Associates Learning	accuracy	462	-0.89	-1.85; 0.08	0.07	**-1.73**	**-3.10; -0.36**	**0.01**
Spatial Working Memory	accuracy	476	-1.15	-2.48; 0.17	0.09	0.43	-1.44; 2.31	0.65
	strategy	477	0.02	-0.32; 0.36	0.91	-0.32	-0.81; 0.17	0.20

**Adjusted for age, grade, sex, area, head injury, smoke, alcohol, drugs, farm residence, mobile phone problematic use score, mobile phone ownership, mother employment, mother education, home language, household size, government grant, repeated grade*, preschool, learner support

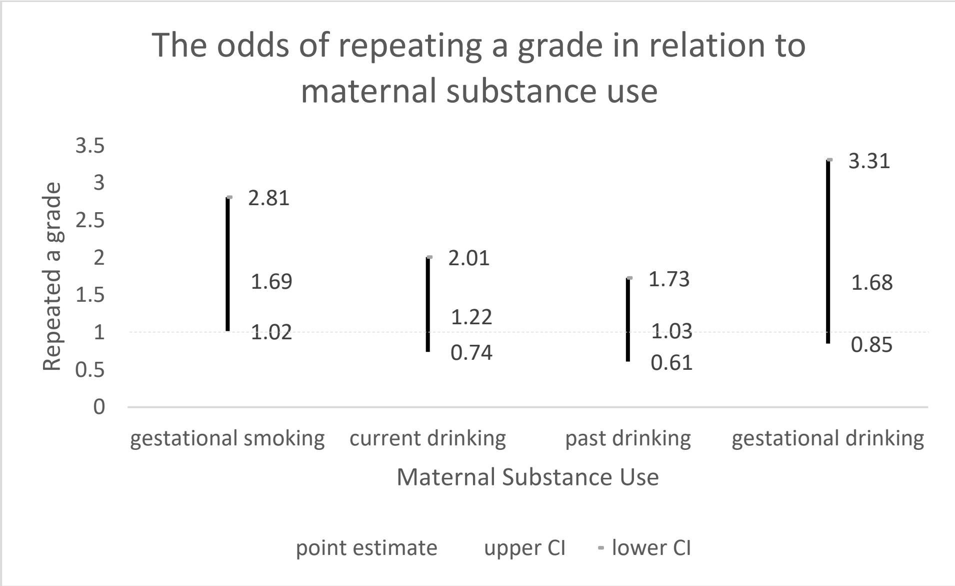

Figure 1 Odds ratio for a child repeating a grade in relation to maternal smoking and drinking behavior during and post pregnancy .

The Figure 1 depicts a significant odds for repeating a grade [1.69; (2.81; 1.02)] for those exposed to maternal gestational smoking and a non-significant odds for those whose mothers reported maternal drinking [1.68; (3.31; 0.85)] compared to those whose mothers reported no gestational smoking or drinking.

4.5 Discussion

In this study we explored the effect of maternal alcohol use and smoking on child cognition, using self-reported data on four exposure proxies, six cognitive outcomes and one health symptom, in a sample of rural school going children and their parent or guardian. Of the 482 parents/guardians who completed the survey, 29% reported current drinking 27% reported past drinking and 10% reported maternal drinking, while more than 50% in each group report gestational smoking (31%). The study sample was gender-balanced (52% male; 48% female) and child participants were aged between 9-16 years old. Maternal past and current drinking significantly reduced child rapid visual processing accuracy in attention [Beta (-0.03); CI (-0.05;-0.004)] and maternal maternal drinking significantly reduced spatial working memory [-0.59; (-1.02; -0.15)]. Heavy (>5 cigarettes per day) maternal gestational smoking significantly lowered child performance on the paired associated learning in memory task [-1.69; (-3.05; -0.33)] and health related quality of life [-3.41;(-6.64; -0.17)]. A child was 70% more likely to repeat a grade [1.69; (2.81-1.02)] if exposed to maternal gestational smoking and maternal drinking [1.68; (3.31-0.85)] than those who were not exposed. There were also several non-significant negative associations between maternal drinking behaviours and child cognition.

The high proportion of alcohol use among mothers in the rural areas of the WC are likely to be related to the wide range of adverse socio-demographic factors that mothers experience in this area, which arguably exist as legacies of both apartheid and the 'dop system,' - the practice of remunerating farmworkers with alcohol (May et al. 2005; London 2005).

Interestingly, animal studies are able to independently assess the exposure of prenatal stress and exposure of prenatal alcohol use from the effect of drinking. A study on moderate prenatal alcohol exposure during pregnancy in monkeys found the same effect of reduced rapid visual processing performance as in our study as their results on reduced orientation (visual orienting and attention) (Coe et al., 2010).

Most importantly our results provide further insight to results of previous epidemiological studies which have shown that alcohol intake during pregnancy was significantly associated with lower cognition in children. In Lebanon lower cognition in children was associated with alcohol intake during pregnancy (-1.07; [−2.10; -0.06]) (Hallit et al. 2019). Spatial working memory in adolescents between 12-14 years old was negatively affected by maternal drinking pregnancy (Spadoni et al. 2008). Additionally, both attention (which is required for memory) and memory were reduced in 7.5 years old as a results of prenatal exposure to alcohol (Burden et al. 2005). A follow-up study investigating different exposed groups according to frequency and quantity of maternal drinking amongst low middle income populations and its long-term effect at school age, observed that both exposed groups had identified deficits in sequential memory processes compared to the non-drinkers (Coles et al. 1991) study (N=68) conducted within the rural Western Cape in South Africa, found a significant association (p<.01) between exposure to alcohol in utero and poorer performance on tests of practical reasoning (assessed using the Griffiths Mental Development Scales). This study therefore adds to the literature as it found consistent negative associations between prenatal maternal alcohol consumption and six cognitive outcome scores in the rural Western Cape of South Africa.

Interestingly, some studies have shown that males are affected more than females in relation to gestational substance use, which was further observed in our sensitivity analysis (Table S7) that males rather than females are significantly affected by maternal drinking in memory (-0.68; [-1.30; -0.06]) (Mortensen et al 2005). Additionally, in relation to maternal drinking the younger age group rather than the older age group is significantly affected in HRQol (-6.04, [-10.05; -2.03]), although such a pattern was not observed for cognitive functions.

There has been different conclusions on an association between prenatal exposure to maternal smoking on the long-term cognitive impairment of offspring, mostly due to insufficient control of confounding including parent factors such as education and other substance use exposures, to detect an effect (Batty et al. 2006; Breslau et al. 2009; Huijbregts et al. 2006; Kafouri et al. 2009; Lawlor et al. 2006) In line with our study, the most consistent findings amongst previous studies are poor academic achievement and intelligence (Clifford et al. 2012).

In addition, maternal smoking has been associated with psychiatric disorders and behavioral problems in this age group (Ramsay et al. 2016). Studies have also found a dose-response associations between exposure to maternal smoking and lower IQ scores of their children (Mortensen et al. 2005).[2] In relation to these studies since our study controlled sufficiently for the main confounding, we have in parallel to existing studies found results on the very same CANTAB test on the same functioning of Paired Associates Learning in memory in a Finnish study with matched sample of young adult offspring exposed to gestational smoking (-0.052) compared to those who were not (0.039).[34] This study notes, that they may not have reached significance due to the smaller sample size of 550 per group that is required to detect an effect. While rodent studies have observed this congruent dose-response relation, since only those studies that experimented with chronic exposure of nicotine in mice, which found impairment in working memory and increased anxiety (Bellés et al. 2016; Hayase 2013). These studies are consistent with our significant findings on lowered HRQOL and memory impairment from high dose exposure to maternal gestational cigarette use.

In a case control study, smoking was highly associated with mothers who binge drink during pregnancy and whose children were diagnosed with FASD in South Africa (May et al. 2006). This study does differentiate between the spectrum of full FASD, FAS and PFAS (Partial FAS) and the effect was dependent on the trimester and frequency of alcohol use. In a metric of different factors of drinking patterns of mothers of pre-school children, an association was found between mothers who showed high characteristic features of maternal drinking (Chiodo et al. 2009). Interestingly, a study in Michigan was conducted to identify the “neurobehavioral profile” of prenatally exposed children who did not present with dysmorphic features and findings are parallel to our results with regard to the exact toxicant affecting the exact subtest and domain of the brain (Jacobson 2008). Alcohol exposure was associated to slower processing speed, while PCBs (Polychlorinated Biphenyls) and drugs was associated to memory impairment (Adnams et al. 2001).

Moreover, this study provides more insight to research done in the WC, which found a significant association between current maternal drinking and child neurobehavioural and neurodevelopmental disorders (BDDs) (OR: 2.98, CI: 1.02-8.70), in the current study it was found that children of mothers who reported current drinking performed worse (on average, see Table 2) on four out of the six EF subtests, compared to mothers who did not report current drinking (Katwan et al. 2011).

With regards to past maternal drinking, the patterns in performance across the EF subtests in the current study are less consistent and appear to deviate from what has been seen in previous local research. Specifically, a smaller research study in the WC (N=110) found past maternal drinking (in the last 6 months) to be associated (OR: 3.00, CI: 1.12, 8.03) with child BDDs (Katwan et al. 2011), and a larger study done in Kwazulu-Natal (N=1505) found maternal hazardous drinking (HD) to be significantly associated with poorer performance on tests of child neurocognitive functioning (assessed using the KABC-II) (Rochat et al. 2019). These non-significant findings are arguably due to the small effect sizes (Cohen's f^2) found across each of the models in this study , which should be explored in future local research studies which employ larger samples (Ellis & Steyn, 2003). The small effect sizes found in this study contrasts somewhat with the medium effect sizes (adjusted ORs > 3.00) found in previous local research by Katwan and colleagues (2010) (Chen, Cohen, & Chen, 2010). This contrast could be due to the fact that this study did not examine a diagnosable neurocognitive outcome such as BDD but rather examined child cognitive outcomes more broadly, for which the effects of the maternal alcohol use behaviours examined may be more subtle (Katwan et al. 2011).

Farm and non-farm residence further accounted for non-significant lower cognitive performance across the models, with significant differences observed for example in (-5.46) in multi-tasking accuracy amongst those living on a farm compared to those not living on a farm. This is consistent with findings from our recent results on the association between pesticide related exposure activities and neurodevelopment in this cohort (Chetty-Mhlanga et al. 2021).

We found smoking during pregnancy as an overall significant predictor of lowered cognitive performance, with an observed significantly lowered performance in the domain of memory. Interestingly, the same predictor for lowered functioning in this area, was significantly related to child participant smokers in this model.

A notable strength of this study is that it adds to the limited body of local research literature regarding the impacts of different types of maternal drinking behaviours (apart from maternal drinking) on child neurocognitive outcomes and under researched area on small effects or symptoms of FASD. The use of the CANTAB in this study is an additional strength, as this electronic battery has been shown to be especially sensitive to variations in child neurocognitive outcomes, and specifically small effect differences in a rural context. Including co-exposures and three to four different behavioral substance use proxies is a strength, lowering the potential of residual confounding in the observed pattern of findings.

However, although this study has several strengths, a limitation includes a potential lack of power to detect the small effect sizes found during modelling due to potential under-reporting of maternal drinking behaviors and the use of self-report measures which are known to be subject to response bias. Another limitation of this research relates to its cross-sectional design which means that the temporality of the relations between the exposures and the outcome (child cognition) of interest requires follow-up data to confirm the identified patterns of association.

4.6 Conclusion

The findings of the current study provide further insights into the impacts of different types of maternal substance use behaviours on developmentally sensitive child neurocognitive outcomes within the context of a LMIC, South Africa. Consistent negative and some significant associations were found between maternal alcohol use and child neurocognitive outcomes and quality of life. Additionally some significant negative associations were found between maternal smoking and child neurocognitive outcomes and quality of life. Further longitudinal analysis is warranted. Policies are to be strengthened to avoid the use of substances during pregnancy and support mothers to limit their use before pregnancy, while screening measures by the WHO should be enforced in all clinics during pre-natal regular check-ups. Additionally, physical exercise and play regimes are suggested as a supportive tool for coping for children in these chronic environments.

Contributors

AD, MR, PV and SM were involved with the conceptualization and formal statistical analysis of the paper. AD and MR are the principal investigators. SM is responsible for the original draft and together with AD, MR and PV the editing thereafter. AD, and PV were responsible for the project administration of the study. All authors reviewed the final versions.

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4.8 Supplementary Material

Maternal alcohol-use and smoking behaviors on the neurocognitive function of school-children in the rural Western Cape

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Table S1: Overview of CANTAB test battery

	Cognitive domain	Test	Cognitive function	Outcome	Duration of test
1	Processing speed including visual motor integration	Reaction Response (RR)	Perception of visual stimuli, response to visual stimuli and execution of motor action	movement time, reaction time and response accuracy;	6 minutes
		Motor Screening (MS)	Sensorimotor or perceptual motor speed and comprehension difficulties	Time lapse between display to response; number of correct and incorrect responses	2 minutes
2	Memory including executive Functioning	Spatial Working Memory (SWM)	Manipulation of visuo-spatial information, executive demands of strategy (reasoning, decision making and behaviour), parts of short-term memory (holding) concerned with immediate conscious perceptual and linguistic processing	Visits, re-visits and searches for boxes	5 minutes
		Paired Associate Learning (PAL)	Visual memory and new learning, episodic memory (collection of past, personal experience that occurred at a particular time and place with associated emotions)	Incorrect selection, adjustment, problem solving and memory of selection	8 minutes
3	Attention	Multi-tasking (MTT)	Attentional set-shifting, cognitive flexibility and lateralization	Congruency and latency during change of instructions	8 minutes
		Rapid Visual Information Processing (RVP)	Sustained attention and continuous performance, impulse control or inhibition	Sensitivity to target and correct responses	7 minutes

Table S2: CANTAB outcome variable analysis – the number of participants categorized as missing and or outlier

	No. of participants	No. Missings	No. Outliers (3.25 SD above or below the mean)	Resolved
EXPOSURES				
Geronimo	0			
MPPUS-10	5	1 out of 10 items		Item imputation
OUTCOMES				
Hit6	2	all 6 items		Omitted from analysis
HRQOL	4	1 out of 5 items		Item imputation
Sleep Disturbance	3	all 4 items		Added to none category
CANTAB				
Processing Speed				
Motor screening	16	5	11 (<3.25)	Removed from analysis
Reaction Time	40	2	38 (>3.35)	Removed from analysis
Attention				
RVIP Processing	20	17	3 (<3.25)	Removed from analysis
Multi-tasking	15	6	9 (>3.25)	Removed from analysis
Memory				
PAL	29	3	26 (<3.25)	Removed from analysis
Spatial Working Memory	10	3	3 (2>3.25; 1<3.25)	Removed from analysis

Table S3: Demographic comparison of the cognitive performance variables in relation to sex and grade for the full cohort of children

Neurocognitive Outcomes	Mean (SD)	Sex (F) Mean (SD)	Sex (M) Mean (SD)	Grade (1-2) Mean (SD)	Grade (4-6) Mean (SD)	Grade (7-9) Mean (SD)	Min-Max
PROCESSING SPEED							
1. Motor Screen Speed (tasks/s)	*1.12 (0.4)	**1.15** (0.40)	1.07 (0.39)	1.04 (0.40)	1.13 (0.39)	1.16 (0.40)	0.27-2.11
2. Motor Screen Accuracy (hits)	9.88 (0.84)	9.88 (0.82)	9.88 (0.86)	9.51 (1.66)	9.94 (0.58)	9.97 (0.24)	0-10
3. Reaction Time Speed (task/s)	*4.35 (1.18)	4.18 (1.1)	4.53 (1.04)	4.17 (1.07)	4.43 (1.08)	**4.16** (4.16)	0.53-9.09
4. Reaction Time Accuracy (hits)	24.87 (7.28)	**24.94** (7.79)	24.78 (6.68)	23.60 (7.88)	25.08 (7.02)	25.25 (7.63)	0-30
ATTENTION							
5. Rapid visual info processing speed (tasks/s)	*2.39 (0.73)	2.34 (0.69)	2.43 (0.76)	2.37 (0.87)	2.35 (0.68)	2.52 (0.75)	0.57-5.29
6. Rapid visual info processing accuracy (hits)	0.81 (0.11)	**0.83** (0.11)	0.81 (0.11)	0.76 (0.12)	0.83 (0.11)	0.85 (0.10)	0.41-0.99
7. Multi-tasking speed (tasks/s)	*1.33 (0.26)	1.31 (0.25)	1.35 (.27)	1.25 (0.33)	1.32 (0.25)	1.41 (.23)	0.72-4.20
8. Multi-tasking accuracy (hits)	120.80 (19.33)	119.85 (18.84)	121.87 (19.83)	114.75 (16.74)	120.04 (19.28)	129.46 (19)	54 -158
MEMORY							
9. Paired associates learning accuracy (hits)	11.62 (4.21)	**11.65** (4.04)	11.59 (4.37)	10.15 (4.77)	11.84 (4.06)	12.18 (3.91)	0-20
10. Spatial working memory accuracy (hits)	18.80 (5.44)	18.64 (5.27)	18.97 (5.62)	17.86 (5.24)	18.60 (5.28)	20.43 (5.87)	0 -41
Total (n)	**1001**	**526**	**471**	**161**	**665**	**171**	

(ms)- milliseconds; (hit) -the number of correct hits
**the latency in milliseconds per task was inverted to a speed measure, then converted to 1/seconds*

Table S4: Socio-economic status variables stratified by area for the subgroup used in the sensitivity analysis

Variable	**Choice Categories**	**Frequency (%)**	**Area 1 (%)**	**Area 2 (%)**	**Area 3 (%)**	**Chi^2**
		Total (N=482)	**(n=105)**	**(n=139)**	**(n=238)**	**P-value**
maternal employment	Unemployed/Other	175 (36.3)	51 (48.6)	71 (51.1)	53 (22.3)	**<0.01**
	Employed	307 (63.7)	54 (51.4)	68 (48.9)	185 (77.7)	
maternal education	<=primary	199 (41.3)	33 (33.3)	44 (31.7)	120 (50.4)	**<0.01**
	>=secondary	283 (58.7)	70 (66.7)	95 (68.4)	118 (49.6)	
home language	Afrikaans	317 (65.8)	98 (93.3)	139 (100)	80 (33.6)	**<0.01**
	Non-Afrikaans	165 (34.2)	7 (6.7)	0 (0)	158 (66.4)	
household size	2-4members	182 (37.8)	32 (30.5)	34 (24.5)	116 (48.7)	**<0.01**
	5-6members	183 (37.9)	35 (33.3)	55 (39.6)	93 (39.1)	
	7+ members	117 (24.3)	38 (36.2)	50 (36)	29 (12.2)	
government grant	childsupportgrant	329 (68.2)	53 (50.5)	90 (64.8)	186 (78.2)	**<0.01**
	other grant	105 (21.8)	35 (33.3)	39 (28.1)	31 (13.0)	
	no grant	48 (10)	17 (16.2)	10 (7.2)	21 (8.8)	

Table S5: Linear regression analysis results – associations of three maternal drinking exposures (Yes/No) with seven cognitive outcome scores. Beta refers to a difference in scores between exposed and unexposed study participants.

			Current drinking (n=141)		Past drinking (n=130)		Gestational drinking (n=48)	
	Score	N	Beta (β) 95% CI	Beta (β) 95% CI*	Beta (β) 95% CI	Beta (β) 95% CI*	Beta (β) 95% CI	Beta (β) 95% CI*
Health Related Quality of Life		482	-1.52 -3.54; 0.49	-1.51 -3.54; 0.52	1.88 -0.14; 3.91	1.77 -0.28; 3.81	-2.16 -5.08; 0.75	-2.74 -5.74; 0.26
Processing Speed								
Motor Screening	Speed (seconds)	482	-0.03 -0.11; 0.05	-0.04 -0.12; 0.04	-0.02 -0.11; 0.06	-0.02 -0.11; 0.06	-0.01 -0.13; 0.11	-0.01 -0.14; 0.11
Reaction Response	Speed	458	-0.08 -0.30; 0.14	-0.10 -0.32; 0.13	0.09 -0.13; 0.32	0.07 -0.16; 0.30	-0.15 -0.48; 0.17	-0.19 -0.52; 0.15
Attention								
Rapid Visual Processing	Speed	472	-0.08 -0.23; 0.07	-0.07 -0.23; 0.08	-0.04 -0.19; 0.11	-0.01 -0.17; 0.14	0.02 -0.19; 0.24	0.04 -0.19; 0.26
	Accuracy (hits)	473	**-0.03 -0.05; -0.004**	**-0.03 -0.05; -0.004**	**-0.03 -0.05; -0.002**	**-0.03 -0.05; -0.004**	-0.01 -0.04; 0.03	-0.01 -0.04; 0.03
Multi-tasking	Speed	474	-0.003 -0.04; 0.04	-0.02 -0.06; 0.02	0.02 -0.02; 0.06	0.02 -0.02; 0.06	0.02 -0.04; 0.08	0.01 -0.05; 0.07
	Accuracy	477	-1.93 -5.91; 2.04	-1.62 -5.68; 2.44	-0.11 -4.12; 3.91	-0.16 -4.25; 3.93	-4.43 -10.14; 1.28	-4.04 -10.00; 1.91
Memory								
Paired Associates Learning	Accuracy	462	-0.33 -1.15; 0.49	-0.38 -1.22; 0.46	0.06 -0.77; 0.89	0.04 -0.81; 0.88	0.27 -0.94; 1.49	0.23 -1.04; 1.49
Spatial Working Memory	Accuracy	476	1.00 -0.12; 2.13	1.03 -0.12; 2.18	0.46 -0.68; 1.61	0.45 -0.72; 1.62	0.16 -1.47; 1.79	0.56 -1.13; 2.26
	Strategy	477	0.28 -0.01; 0.58	0.27 -0.26; 0.57	-0.08 -0.38; 0.22	-0.04 -0.35; 0.26	**-0.53 -0.95; -0.11**	**-0.59 -1.02; -0.15**

Adjusted for age, grade, sex, area, head injury, smoke, alcohol, drugs, farm residence, mobile phone problematic use score, mobile phone ownership smoking_pregnancy

**Adjusted+ = Adjusted+mother employment, mother education, home language, household size, government grant, repeated grade*, preschool, learner support

Table S6: Linear regression analysis results – associations of three maternal drinking exposures (Yes/No) with seven cognitive outcome scores, stratified by sex. Beta refers to a difference in scores between exposed and unexposed study participants.

		N=482	**Current drinking (n=141)**		**Past drinking (n=130)**		**Gestational drinking (n=48)**	
	Score	Male; Female	Male Beta (β) 95% CI	Female Beta (β) 95% CI	Male Beta (β) 95%CI	Female Beta (β) 95% CI	Male Beta (β) 95%CI	Female Beta (β) 95% CI
Health Related Quality of Life		231; 251	-1.06 -3.88; 1.74	-1.58 -4.67; 1.52	0.07 -2.90; 3.05	**3.42** **0.47; 6.36**	-2.66 -7.00; 1.68	-3.26 -7.67; 1.16
Processing Speed								
Motor Screening	Speed (seconds)	231; 251	0.02 -0.11; 0.14	-0.10 -0.21; 0.03	0.05 -0.07; 0.18	-0.11 -0.23; 0.003	0.03 -0.16; 0.21	-0.05 -0.22; 0.13
Reaction Response	Speed	220; 238	-0.05 -0.37; 0.26	-0.13 -0.47; 0.22	0.26 -0.07; 0.59	-0.11 -0.45; 0.22	-0.05 -0.54; 0.44	-0.32 -0.82; 0.18
Attention								
Rapid Visual Processing	Speed	227; 245	-0.01 -0.24; 0.22	-0.13 -0.35; 0.09	-0.06 -0.30; 0.18	0.01 -0.20; 0.23	0.09 -0.26; 0.44	0.004 -0.31; 0.31
	Accuracy (hits)	228; 245	-0.03 -0.06; 0.01	-0.02 -0.06; 0.01	-0.03 -0.07; 0.002	-0.02 -0.05; 0.01	0.00 -0.05; 0.05	-0.02 -0.07; 0.03
Multi-tasking	Speed	247; 227	-0.003 -0.04; 0.04	-0.04 -0.10; 0.02	0.04 -0.02; 0.11	-0.01 -0.07; 0.05	0.01 -0.09; 0.10	0.02 -0.06; 0.11
	Accuracy	250; 227	0.88 -4.70; 6.47	-3.98 -10.10; 2.14	-3.95 -9.85; 1.94	2.30 -3.52; 8.13	-6.33 -14.88; 2.22	-1.03 -9.69; 7.63
Memory								
Paired Associates Learning	Accuracy	217; 245	-0.38 -1.65; 0.90	-0.39 -1.60; 0.82	-0.30 -1.64; 1.05	0.37 -0.78; 1.53	-1.53 -3.58; 0.52	1.77 0.05; 3.49
Spatial Working Memory	Accuracy	229; 247	0.55 -1.08; 2.19	1.47 -0.27; 3.21	0.61 -1.11; 2.34	0.77 -0.91; 2.43	1.15 -1.37; 3.67	0.47 -1.99; 2.93
	Strategy	229;	0.34 -0.06; 0.75	0.13 -0.33; 0.60	0.04 -0.39; 0.47	-0.09 -0.54; 0.35	**-0.68** **-1.30; -0.06**	-0.50 -1.15; 0.15

Adjusted for age, grade, sex, area, head injury, smoke, alcohol, drugs, farm residence, mobile phone problematic use score, mobile phone ownership smoking pregnancy, mother employment, mother education, home language, household size, government grant, repeated grade, preschool, learner support

Table S7: Linear regression analysis results – associations of three maternal drinking exposures (Yes/No) with seven cognitive outcome scores, stratified by age. Beta refers to a difference in scores between exposed and unexposed study participants

		N=482	**Current drinking (n=141)**		**Past drinking (n=130)**		**Gestational drinking (n=48)**	
	Score	9-11y; 12-16y	Age 9-11 Beta (β) 95% CI	Age 12-16 Beta (β) 95% CI	Age 9-11 Beta (β) 95% CI	Age 12-16 Beta (β) 95% CI	Age 9-11 Beta (β) 95% CI	Age 12-16 Beta (β) 95% CI
Health Related Quality of Life		284; 198	**-3.15** **-5.88; -0.41**	2.11 -1.18; 5.39	1.07 -1.70; 3.84	2.91 -0.29; 6.10	**-6.04** **-10.05; -2.03**	3.01 -1.61; 7.63
Processing Speed								
Motor Screening	Speed (seconds)	284; 198	-0.01 -0.11; 0.10	-0.06 -0.21; 0.10	0.03 -0.08; 0.13	-0.09 -0.24; 0.06	-0.07 -0.23; 0.09	0.10 -0.12; 0.31
Reaction Response	Speed	274; 184	-0.06 -0.30; 0.22	-0.08 -0.51; 0.35	0.04 -0.24; 0.32	0.05 -0.37; 0.46	-0.26 -0.67; 0.16	-0.17 -0.77; 0.43
Attention								
Rapid Visual Processing	Speed	276; 196	-0.06 -0.27; 0.13	-0.08 -0.35; 0.19	0.05 -0.15; 0.26	-0.14 -0.40; 0.13	0.16 -0.14; 0.45	-0.18 -0.56; 0.21
	Accuracy (hits)	276; 197	-0.02 -0.06; 0.01	-0.03 -0.07; -0.003	-0.02 -0.05; -0.01	**-0.04** **-0.08; -0.01**	0.01 -0.04; 0.05	-0.03 -0.08; 0.02
Multi-tasking	Speed	278; 196	-0.04 -0.10; 0.004	-0.02 -0.06; 0.02	0.04 -0.04; 0.11	0.02 -0.03; 0.08	0.03 -0.05; 0.10	0.01 -0.06; 0.09
	Accuracy	279; 198	-4.07 -9.11; 0.98	2.00 -5.46; 9.46	0.22 -4.86; 5.30	0.05 -7.25; 7.35	-6.35 -13.72; 1.02	3.43 -7.06; 13.92
Memory								
Paired Associates Learning	Accuracy	268; 194	-0.66 -1.75; 0.43	-0.30 -1.81; 1.21	0.09 -0.01; 1.19	-0.37 -1.83; 1.09	0.59 -1.08; 2.26	-0.31 -2.41; 1.79
Spatial Working Memory	Accuracy	279; 197	**1.49** **0.06; 2.92**	0.70 -1.40; 2.79	0.41 -1.04; 1.87	0.85 -1.20; 2.90	0.44 -1.67; 2.55	0.42 -2.53; 3.38
	Strategy	279; 198	0.31 -0.07; 0.69	0.13 -0.42; 0.69	0.02 -0.36; 0.41	-0.17 -0.71; 0.36	**-0.67** **-1.22; -0.12**	-0.20 -1.00; 0.57

Adjusted for age, grade, sex, area, head injury, smoke, alcohol, drugs, farm residence, mobile phone problematic use score, mobile phone ownership smoking pregnancy, mother employment, mother education, home language, household size, government grant, repeated grade, preschool, learner support

Chapter 5

5. Pesticide exposure and neurobehavior

Association of pesticide exposure-related activities with symptoms and neurocognitive performance of school-children in the rural agricultural farmlands of the Western Cape of South Africa

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Association of activities related to pesticide exposure on headache severity and neurodevelopment of school-children in the rural agricultural farmlands of the Western Cape of South Africa

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A B S T R A C T

Objective: Children and adolescents living in agricultural areas are likely to be exposed to mixtures of pesticides during their daily activities, which may impair their neurodevelopment. We investigated various such activities in relation to headache severity and neurodevelopment of school-children living in rural agricultural areas in the Western Cape of South Africa.

Method: We used baseline date from 1001 school-children of the Child Health Agricultural Pesticide Cohort Study in South Africa (CapSA) aged 9–16 from seven schools and three agriculture areas in the Western Cape. Questionnaires were administrated to assess activities related to pesticide exposure and health symptoms addressing four types of activities: 1) child farm activities related to pesticide handling, 2) eating crops directly from the field, 3) contact with surface water around the field, and 4) seen and smelt pesticide spraying activities. Neurocognitive performance across three domains of attention, memory and processing speed were assessed by means of an iPad-based cognitive assessment tool, Cambridge Automated NeuroPsychological Battery (CANTAB). Headache severity was enquired using a standard Headache Impact Test (HIT-6) tool. Cross-sectional regression analysis was performed.

Results: About 50% of the cohort report to have ever been engaged in activities related to pesticide exposure including farm activities, eating crops directly from the field and leisure activities. Headache severity score was consistently increased in relation to pesticide-related farm activities (score increase of 1.99; 95% CI: 0.86, 3.12), eating crops (1.52; 0.41, 2.67) and leisure activities of playing, swimming or bathing in nearby water (1.25; 0.18, 2.33). For neurocognitive outcomes, an overall negative trend with pesticide exposure-related activities was observed. Among others, involvement in pesticide-related farm activities was associated with a lower multitasking accuracy score (2.74; 5.19, 0.29), while lower strategy in spatial working memory (0.29; 0.56; 0.03) and lower paired associated learning (0.88; 1.60, 0.17) was observed for those who pick crops off the field compared to those who do not pick crops off the field. Eating fruits directly from the vineyard or orchard was associated with a lower motor screening speed (0.06; 0.11, 0.01) and lower rapid visual processing accuracy score (0.02; 0.03, 0.00).

Conclusions: Children who indicate activities related to pesticide exposure may be at higher risk for developing headaches and lower cognitive performance in the domains of attention, memory and processing speed. However, self-reported data and cross-sectional design are a limitation. Future research in CapSA will consider pesticide exposure estimations via urinary biomarkers and longitudinal assessment of cognitive functions.

Abbreviations: CapSA, Child Health Agricultural Pesticide Cohort Study in South Africa; CANTAB, Cambridge Automated NeuroPsychological Battery; HIT-6, Headache Impact Test; LMICs, Low- and Middle-Income Countries.

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1. Background

Children living in agricultural areas are likely to be exposed to various neurotoxic pesticides during their daily lives. The most vulner- able populations are the farmworkers and families in low- and middle- income countries (LMICs) (Fenske et al., 2000). Children are expected to be more vulnerable to environmental exposure than adults due to their still developing organs and higher dermal contact including: hand- to-mouth activities, larger food intake per unit height and body weight, breathing in relatively larger volumes of air, and playing in more haz- ardous zones for example in outdoor activities with closer contact to the ground (Fenske et al., 2000; Bellinger, 2018). Neurodevelopmental disorders linked to early exposures of pesticides include Autism (Sagiv Sharon et al., 2018), Attention Deficit Hyperactivity Disorder (ADHD) (Yu et al., 2016), poorer social behavior, lower Intelligence (IQ) and worse behavioral regulation (Furlong et al., 2017; Gonzalez-Casanova et al., 2018). The majority of evidence has focused on pre-natal expo- sure to pesticides and the effect on neurodevelopment of children up to seven years old since the developing brain is most vulnerable at this stage to all three processes of development including building neurons, synaptology and mylenation (Bellinger, 2018; Abdel Rasoul et al., 2008). However, older children and adolescents in rural areas engage in work and leisure time activities and thus may be exposed to relatively high pesticide levels. Although less studied, they are vulnerable to chronic health symptoms as recently observed in two cohorts of ado- lescents working as pesticide applicators in Egypt with consequent neurobehavioral deficits in processing speed, attention, memory and neurological symptoms (Ismail et al., 2017).

Children and adolescents are thus exposed to a mixture of different pesticides (Dalvie et al., 2011; English et al., 2012). Organophosphates (OPs) are widely used for outdoor application, but are also used indoors for pesticide control (Fenske et al., 2000). OP's, specifically Chlorifyros, affects the brain in both an acutely toxic manner, irreversibly inhibiting the Acetacholenestraasse (ACHE) to break down the neurotransmitters, but at the same time, chronic exposure to this pesticide may also interfere with the brain at less severe structural processes (Li et al., 2019). A recent study on post-natal exposure to low-level Chlorpyrifos in children confirms the inhibition of cholinesterases (CHe) through an alternate target compared to that of high dose exposure on CHe inhi- bition (Perez-Fernandez et al., 2020). A similar study on rats confirmed this distinction, revealing that compared to the acute high-dose expo- sure to the OP Malathion effect inhibiting AChE activity; long-term exposure effected the Spatial Working Memory of rats (dos Santos et al., 2016). Additionally, the association of headache symptoms to occupational OP exposure in children are suggestive of the consequen- tial chronic effects of pesticides on the nervous system (Rastogi et al., 2010).

South Africa, an upper middle-income country has the highest application rates of pesticides in Sub-Saharan Africa (Quinn, et al., 2011). Over 3000 different types of pesticide product formulations are registered, including the possible neurotoxic and endocrine disrupting chemicals (EDCs) active ingredients bifenthrin, chlorpyrifos, cyper- methrin and mancozeb (Dabrowski, 2015; DAFF, 2010). In the Western Cape, a wide range of pesticides have been detected in the environment and in exposed persons, whose modes of uptake and level of toxicity are very different (Fuhrimann et al., 2020; Curchod et al., 2020; Dalvie et al., 2003; Dalvie et al., 2009). A recent study in the Western Cape in 2017, showed that the dominating stone fruit, grapes and wheat farms used up to 96 active ingredients (47 fungicides, 31 insecticides and 18 herbicides). Most common active ingredients which were used include 2,4-d, bromoxynil, chlorpyrifos, glyphosate, mancozeb, MCPA, penco- nazole, spiroxamine. This intensive farming system in the Western Cape also lead to environmental contaminants. For example, levels of pesti- cides in surface water that exceeded environmental quality standards (i. e., for imidacloprid, thiacloprid, chlorpyrifos and acetamiprid, terbu- thylazine) (Curchod et al., 2020) or the persistent presence of pesticides in ambient air (e.g., atrazine, carbaryl, chlorpyrifos or malathion) (Fuhrimann et al., 2020). In addition, previously banned but environmentally-persistent pesticides such as endosulfan were frequently detected in drinking and surface water (Dalvie et al., 2003; Dalvie et al., 2009). Ultimately human exposure to organophosphates and endosulfan metabolites have also been reported in farm workers and residents of the rural Western Cape (Dalvie et al., 2014; Dalvie et al., 2011). However, there is a lack in human exposure data to pesticide mixtures or assessments of activities which may lead to mixed exposure situations specifically in resident populations.

This study aims at investigating the association between activities related to pesticide exposure, headache and neurocognitive functioning of children and adolescents in three agricultural areas in the Western Cape of South Africa. Our hypothesis is that children who engage with pesticide-related activities, have a higher chronic pesticide exposure and thus lower cognitive functioning and increased health symptoms than those who do not.

2. Methods

2.1. Study design

This study used baseline data from 1001 children within the Child Health Agricultural Pesticide Cohort Study in South Africa (CapSA) (Chetty-Mhlanga et al., 2018). The research was conducted in three areas with distinct agriculture production in the Western Cape between 2017 and 2019. The areas include the Hex River Valley (mainly table grapes), Grabouw (mainly stone fruits) and Piketberg (mainly cereals). Children aged nine to 16 years old were recruited from seven schools attending grades two to nine. To ensure a pesticide exposure contrast in terms of proximity to agriculture fields, children were purposely enrolled from farms and villages. Children were interviewed at baseline in 2017 on the school premises using the smartphone-based application Open Data Kit (ODK) to enquire about their exposures and headache symptoms. Thereafter participants were assessed on cognitive func- tioning, individually for a 40 -minute period via a neurocognitive soft- ware assessment tool on tablets. In addition an interview was conducted between 2018 and 2019 with the guardians (n = 482) of the children at their home. The interview covered questions on socio-demographics including education, employment, language, household size.

2.2. Health outcomes

2.2.1. Two standardized health outcome tools were used for the assessment of health outcomes including

2.2.1.1. Headache scores. The headache Impact Test (HIT-6) was included in the participant survey, with six questions on the severity of headaches using a five-point Likert scale for responses ranging from never to always and resulting in a score ranging from 36 to 78 (Kosinski et al., 2003).

2.2.1.2. Neurocognitive assessment. A neurocognitive assessment bat- tery, the Cambridge Automated NeuroPsychological Battery (CANTAB) of six tests across three cognitive domains (memory, attention and processing speed) was conducted (see study protocol paper for descriptive details). (Chetty-Mhlanga et al., 2018). The six CANTAB tests recorded several performance scores, including latency and accuracy for each task within each test: Motor Screening (MS); Reaction Response (RR); Spatial Working Memory (SWM); Paired Associate Learning (PAL); Multi-tasking (MTT); Rapid Visual Information Processing (RVP) (see Supplementary for test description, Table S1) (Chetty-Mhlanga et al., 2018). The latency scores in milliseconds per task were inverted to a speed measure to obtain a near normal distribution of the data. For consistent result presentation inaccuracy scores were converted to accuracy scores by subtracting the inaccuracy score from the maximum achievable score. Outliers were excluded if any value was 3.25 standard deviations above and below the mean.

2.3. Pesticide exposure assessment

We explored the pesticide exposure from the participant surveys by asking about different farm and leisure activities that result in ingestion of potentially contaminated water or food, inhalation of gases in air or dust or direct dermal contact with the body.

Specifically the following aspects were inquired in the interview: 1) child farm activities related to pesticide handling; 2) eating crops directly from the field; 3) contact with surface water around the field; and 4) seen and smelt pesticide spraying activities. Involvement in farm activities was defined to have done any of these activities: helped with picking fruits in the field/vineyard/orchard; helped with cleaning farm equipment; assisted in pesticide storage; helped with burning any pesticide or chemical containers and helped with pesticide or chemical spraying, mixing or loading.

To account for any difference between potential acute and long-term exposure, participants were asked about long-term exposure and short-term exposure by enquiring about “ever” exposure as well as exposure “in the last 7 days”.

2.4. Statistical analysis

We conducted linear regression models to calculate associations between pesticide exposure proxies and headache and nine cognitive test scores. Models were a priori adjusted for demographic and lifestyle variables of area, age, grade, sex, head injury (severe head accident or potential Traumatic Brain Injury), smoking, alcohol and drugs. In-depth analysis gave indication of confounding for two lifestyle exposure variables relevant to this cohort: mobile phone ownership and problematic mobile phone use (Chetty-Mhlanga et al., 2020).

For a subset of the cohort (n = 482), additional sociodemographic variables were available from the guardian survey (Chetty-Mhlanga et al., 2018). Thus, an additional analysis was conducted with this subgroup, where models were additionally adjusted for five sociodemographic variables (home language, maternal education, maternal employment, government grant, household size). Further, a sensitivity analysis was conducted with the full cohort on gender and age stratification. All regression models were stratified by two age groups, children (9.0–11.9 years) and adolescents (12.0–16.1).

There was a substantial overlap between the group of recent (“In the past 7 days, how often did you…”) and long-term (“have you ever…”) exposure proxies (Supplementary Fig. 1). For this reason, we only conducted analyses related to ever exposure but not to recent exposure.

In order to evaluate dose-related associations, a separate analysis was done for eating crops from the field/vineyard/orchard in relation to washing behavior and picking crops in relation to wearing Personal Protective Equipment (PPE). For the combination of the exposure variable, “eating crops” and “washing fruits” low exposure (0) corresponds to “never eat fruit” and “always wash fruit”, moderate exposure (1) corresponds to “eat crops from the field and sometimes or always washing fruit”, and high exposure (2) corresponds to “eat fruit and never or rarely washing fruit”. For the combination of the exposure variable “picking crops” and “use of PPE”, low exposure (0) corresponds to “never pick crops”, moderate exposure (1) corresponds to “pick crops with PPE” and high exposure (2) corresponds to “pick crops without PPE”.

3. Results

Table 1 shows the characteristics of the study population, see Supplementary Table S2, stratified by gender and study area. The 1001 school-children aged nine to 16 years (mean: 11; SD: ±1.7) from grades

Table1
Demographics of the children at baseline enrolled in the cohort study in the Western Cape, South Africa between 2017 and 2019, separate for the whole cohort and the sub cohort with guardian interviews.

**TBI –Traumatic Brain Injury*	**Total n (%)**	**Sub-cohort Total n (%)**
TOTAL n (%)	**1001(100)**	**482 (100)**
Age categories		
9–11 years	592 (59.1)	284 (59)
12–14 years	356 (35.6)	164 (34)
15–16 years	53 (5.3)	34 (7)
Grade categories		
2nd-3rd	163 (16.3)	79 (16)
4th-6th	667 (66.6)	310 (64)
7th-9th	171 (17.1)	93 (20)
Head Injury (ever)		
0 (none)	659 (65.9)	304 (63)
1 (fell & hit head)	230 (23.0)	116 (24)
2 (potential TBI*)	112 (11.2)	62 (13)
Smoke (ever)		
No	854 (85.4)	410 (85)
Yes	147 (14.7)	72 (15)
Alcohol Use (ever)		
No	851 (85.1)	395 (82)
Yes	150 (15.0)	87 (18)
Drug Use (ever)		
No	976 (97.6)	468 (97)
Yes	25 (2.5)	14 (3)
Indoor leisure activities		
Mobile Phone Use (current)		
No	683 (68.3)	350 (73)
Yes	318 (31.8)	132 (27)
Electronic Media Use (current)		
No	540 (54.0)	284 (59)
Yes	461 (46.1)	198 (41)

two to nine (5; ±1.5) were distributed almost equally over three study areas and across gender (Table S2). Guardian interviews were conducted with 482 participants. One third (32%) use a mobile phone for calls, texting or the internet and 46% engage in screen time (e-media device and the internet). Previous head injury was reported by 34%, while 15% are smoking, 16% drink alcohol and 2% consume other drugs.

Regarding pesticide exposure (Supplementary Table S3), around 46% of the children live on farms, with the highest proportion (62%) living on farms in the Grabouw area. In total, 47% and 66% of the participants have parents or family members who work on a farm respectively. Pesticide spraying was reported by 80% of the study participants, with the highest in the Grabouw area, predominantly via tractor spraying while 52% reported smelling pesticide spraying. About 50% of the cohort participated in all three farm and leisure activities with significant differences between study areas and gender (Supplementary Table S4).

Figs. 1 and 2 illustrate the pesticide exposure proxies across the three study areas. In total, 24.6% engaged in pesticide-related farm activities, 51.5% are eating crops from the field and 49.4% are swimming in surface water. Picking fruit, cleaning and storing pesticide equipment are the most frequently reported farm activities (47.4%) and are most prevalent in De Doorns. De Doorns was also the area where most children reported engaging in leisure activities, with almost 70% eating crops directly off the field/vineyard/orchard, and over 50% playing, swimming or bathing in nearby water in both De Doorns and Grabouw. Moderate overlap was observed between different exposure proxies as shown in Supplementary Fig. S2.

Table 2 shows the association between change in headache and six cognitive performance outcome scores in relation to farm activities, eating crops and leisure-related activities. The headache impact test score was consistently increased in relation to all three pesticide exposure proxies. Most of the cognitive tests showed a negative association with pesticide exposure although only three associations reached statistical significance; motor screening speed and accuracy of rapid visual information processing in relation to eating crops directly from the

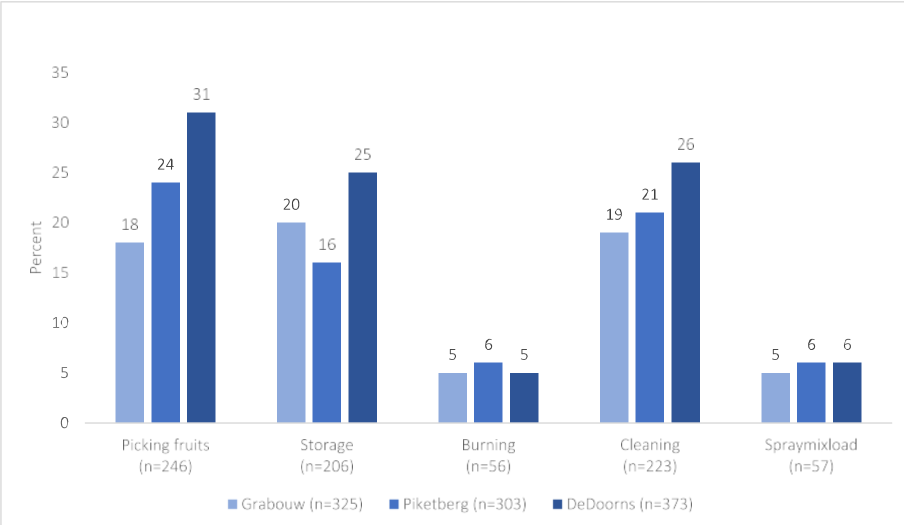

Fig. 1. The individual pesticide-related farm activities which children ever performed stratified across the three agricultural farm areas.

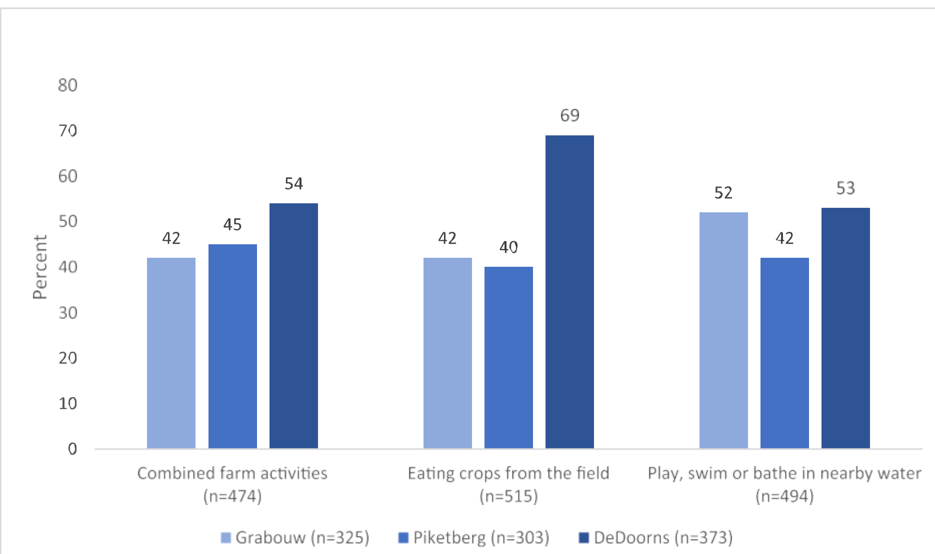

Fig. 2. Pesticide-related farm and leisure time activities which children ever performed stratified across the three agricultural farm areas.

Table 2
Linear regression analysis results from the full sample: associations of three pesticide-related exposures with headache score and six cognitive performance outcome scores. Beta refers to a difference in scores between exposed and unexposed study participants.

Farm activities (n ¼ 474)						**Eating (n ¼ 515)**			**Leisure (n ¼ 494)**		
	Score	N	Beta (β)	95% CI	P-value	Beta (β)	95% CI	P-value	Beta (β)	95% CI	P-value
Symptom											
Headaches	Total	999	**1.99**	**0.86; 3.12**	**<0.01**	**1.52**	**0.41; 2.67**	**<0.01**	**1.25**	**0.18; 2.33**	**0.02**
Processing Speed											
Motor Screening	Speed (seconds)	997	0.04	0.01; 0.10	0.12	**¡0.06**	**¡0.11; 0.01**	**0.02**	0.00	0.05; 0.05	1.00
Reaction Response	Speed	961	0.10	0.24; 0.05	0.18	0.13	0.28; 0.01	0.07	0.07	0.20; 0.07	0.34
Attention											
Rapid Visual Processing	Speed	981	0.04	0.14; 0.06	0.43	0.02	0.12; 0.08	0.70	0.05	0.14; 0.05	0.33
	Accuracy (hits)	984	0.00	0.10; 0.01	0.51	**¡0.02**	**¡0.03; 0.00**	**0.02**	0.00	0.13; 0.01	0.93
Multi-tasking	Speed	986	0.01	0.02; 0.04	0.43	0.00	0.03; 0.02	0.84	0.02	0.04; 0.01	0.27
	Accuracy	994	**¡2.74**	**¡5.19; ¡0.29**	**0.03**	0.04	2.43; 2.51	0.98	1.69	4.09; 0.71	0.17
Memory											
Paired Associates Learning	Accuracy	969	0.44	0.96; 0.08	0.10	0.45	0.96; 0.06	0.08	0.24	0.73; 0.26	0.35
Spatial Working Memory	Accuracy	991	0.03	0.76; 0.69	0.93	0.40	1.11; 0.31	0.27	0.08	0.78; 0.61	0.81
	Strategy	991	0.06	0.25; 0.14	0.56	0.00	0.19; 0.19	0.96	0.17	0.35; 0.01	0.07

*Adjusted for age, grade, sex, area, head injury, smoke, alcohol, drugs, farm residence, mobile phone problematic use score, mobile phone ownership.

field/vineyard/orchard, as well as accuracy of a multitasking test in relation to farm activities.

Model coefficients in the subgroup with additional socio- demographic information (Table 3) were somewhat different from those in the full sample (Table 2), also with wider confidence intervals due to the smaller sample size. However, coefficients did not noticeable vary between the two adjusted models in the same subgroup sample (Table 3) indicating that confounding by socio-demographic factors did not explain these differences.

Analysis of headache and cognitive performance scores in relation to eating crops from the field combined with washing fruit did not indicate hypothesized consistent exposure–response pattern between these exposure proxies and the outcomes (Supplementary Table S5). The headache severity score was significantly lower in the high-exposure group. For cognitive tests, reduced reaction response speed was observed in the moderate-exposure group and increased rapid visual information processing speed in the high exposure group. Further, lower accuracy in a multi-tasking test was observed in the high-exposure group.

Table 4 presents results on the association in headache and cognitive performance scores in relation to picking crops with PPE. The headache score was significantly higher in both, the moderate and the high-exposure groups compared to the reference group. For cognitive functions, two significant negative associations were observed for the moderate-exposure group, with a lower memory accuracy and memory strategy score compared to those who do not pick crops but no significant associations in the high exposure group. Additional adjustment for sociodemographic factors (Table 5) had little impact on the headache and the cognitive testing scores.

Overall, no specific pattern of association is found between the individual farm activities and neurocognitive health outcome scores (see Supplementary Table S7). The headache score is significantly increased for those who store pesticides but not amongst the other farm exposure activities.

Fig. 3 displays the association between differences in headache scores in relation to having seen pesticide spraying in nearby fields and having smelled pesticide after spraying. A significant exposure-repose relationship is observed for the headache score in relation to reported frequency of these environmental exposures. No association is observed between these two environmental exposure proxies and neurocognitive performance. Age stratified analysis did not reveal systematic different association patterns between the 9 to 11 year old and the 12 to 16 year old study participants (Tables S9 and S10). No consistent differences were observed between female and male study participants.

4. Discussion

After using various pesticide related activities and behaviors as a surrogate measure for long-term pesticide exposure, our results suggest an overall negative effect of long-term pesticide exposure on headache and cognitive functioning, although mostly non-significant for the latter.

Characterizing exposure to a broad mixture of pesticides is complex within agricultural communities due to the unknown and unpredictable exposure pathways related to activity patterns of exposed persons, the variety of pesticides used and the intensity at which people are exposed through their environment (Fenske et al., 2000). Previous studies have found high pesticide exposure in farmworkers children due to take-home pesticide exposure (Hyland and Laribi, 2017). A recent study found that urine metabolites were higher in school children who ate fruit at school (Muñoz-Quezada et al., 2019). This corresponds with significant differences in the association of higher pesticide metabolites amongst farmworkers and their families eating vegetables during the harvest season, compared to the vegetable consumption of non-farmworkers (Holme et al., 2016). Similarly, increased biomarkers amongst pre-schoolers living in agricultural areas, is suggestive of increased dietary intake and mobility/activity (Li et al., 2019). These studies support our most consistent association with eating crops from the vineyard or orchard on cognitive functioning. A thesis on vulnerable populations in The Gambia, reveals that the risky practices of agricultural children were reported to include: "not wearing PPE; mixing and applying with bear hands; storing pesticides in the home; inadequately disposing of pesticide containers and wearing shoes in the home after working with pesticides" (Butler-Dawson et al., 2016). This also demonstrates that pesticide exposure is correlated with various behaviors and activities (Li et al., 2019). In our study we thus used characteristics and activities related to pesticides exposure. Many other studies of postnatal exposure focus on metabolites to determine previous exposure. Such biomarkers are doubtless information for exposure

Table 3

Linear regression analysis results from the subgroup with and without adjustment for socio-demographic factors: changes in headache score and 6 cognitive performance outcome scores in relation to three pesticide related exposures between those who engage in these activities and those who do not.

Farm activities (n ¼ 225)					**Eating (n ¼ 273)**		**Leisure (n ¼ 230)**	
	Score	n	Beta (β) (95% CI) Adjusted	Beta (β) (95% CI) Adjusted+*	Beta (β) (95% CI) Adjusted	Beta (β) (95% CI) Adjusted+*	Beta (β) (95% CI) Adjusted	Beta (β) (95% CI) Adjusted+*
Symptom								
Headaches	Total	481	1.04 (0.60; 2.69)	1.21 (0.46; 2.89)	1.59 (0.01; 3.21)	1.59 (0.06; 3.25)	1.07 (0.53; 2.67)	1.05 (0.57; 2.66)
Processing Speed								
Motor Screening	Speed (seconds)	482	**0.10 (0.02; 0.18)**	**0.09 (0.01; 0.17)**	0.03 (0.11; 0.04)	0.01 (0.09; 0.07)	0.02 (0.10; 0.05)	0.02 (0.09; 0.06)
Reaction Response	Speed	458	0.17 (0.38; 0.04)	0.19 (0.40; 0.02)	0.19 (0.39; 0.02)	0.20 (0.40; 0.01)	0.11 (0.31; 0.09)	0.10 (0.31; 0.10)
Attention								
Rapid Visual Info Processing	Speed	472	0.05 (0.09; 0.19)	0.07 (0.07; 0.22)	0.03 (0.11; 0.17)	0.03 (0.11; 0.17)	0.01 (0.15; 0.13)	0.00 (0.14; 0.13)
Multi-tasking	Speed	474	0.00 (0.04; 0.04)	0.00 (0.04; 0.04)	0.00 (0.04; 0.04)	0.00 (0.03; 0.04)	0.03 (0.07; 0.01)	0.03 (0.07; 0.01)
Memory								
Paired Associates Learning	Accuracy (hits)	462	0.09 (0.68; 0.86)	0.04 (0.75; 0.83)	0.64 (1.40; 0.12)	0.63 (1.41; 0.14)	0.22 (0.98; 0.52)	0.17 (0.93; 0.59)
Spatial Working Memory	Strategy	477	0.02 (0.30; 0.26)	0.01 (0.29; 0.27)	0.01 (0.28; 0.26)	0.03 (0.25; 0.31)	0.05 (0.32; 0.22)	0.05 (0.32; 0.21)

Adjusted = sex, age, grade, area, head injury, smoke, alcohol, drugs, farm residence, farm residence, mobile phone ownership, problematic mobile phone use.
*Adjusted+ = Adjusted + mother employment, mother education, home language, household size, government grant, repeated grade, preschool, learner support.
Data presented as the Beta from linear regression models.

Table 4
Linear regression analysis results from the full sample: changes in the headache score and six cognitive performance outcome scores in relation to picking fruits combined with wearing protective equipment.

Picking and Protective wear								
Ref (n = 755)			Moderate Exposure (n = 141)			High Exposure (n = 105)		
		n	Beta (β)	95% CI	P-value	Beta (β)	95% CI	P-value
Health Symptom.								
Headaches	Total	999	**2.57**	**1.02;4.11**	**<0.01**	**1.92**	**0.18; 3.65**	**0.03**
Processing Speed								
Motor Screening	Speed	997	0.04	0.04;0.11	0.30	0.04	0.12; 0.05	0.41
Reaction Response	speed	961	0.02	0.17;0.22	0.80	0.18	0.40; 0.04	0.11
Attention								
Rapid Visual Info Processing	Speed	981	0.12	0.26; 0.01	0.08	0.01	0.14; 0.16	0.86
	accuracy	984	0.00	0.02; 0.02	0.81	0.02	0.04; 0.01	0.16
Multi-tasking	Speed	986	0.02	0.02;0.06	0.33	0.01	0.05; 0.03	0.73
	accuracy	994	1.03	4.48; 2.42	0.56	2.99	6.85; 0.88	0.13
Memory								
Paired Associates Learning	accuracy	968	**¡0.88**	**¡1.60; ¡0.17**	**0.02**	0.30	1.10; 0.50	0.46
Spatial Working Memory	accuracy	990	0.32	0.67; 1.32	0.52	0.40	1.52; 0.71	0.48
	strategy	990	**¡0.29**	**¡0.56; ¡0.03**	**0.03**	0.10	0.20; 0.39	0.51

*Adjusted for age, grade, sex, area, head injury, smoke, alcohol, drugs, farm residence, mobile phone problematic use score, mobile phone ownership. Ref = low exposure "never pick crops", moderate exposure= "pick crops with PPE", high exposure ="pick crops without PPE".

Table 5
Linear regression analysis results from the subgroup with and without adjustment for socio-demographic factors: changes in the headache score and six cognitive performance outcome scores in relation to picking fruits combined with wearing protective equipment.

Picking and Protective wear						
Ref (n = 366)			Moderate Exposure (n = 68)		High Exposure (n = 48)	
		n	Beta (β) 95% CI Adjusted	Beta (β) 95% CI Adjusted+*	Beta (β) 95% CI Adjusted	Beta (β)95% CI Adjusted+*
Health Symptom.						
Headaches	Total	481	**3.04**	**3.37**	0.98	1.19
			0.75; 5.34	**1.01; 5.72**	1.58; 3.54	1.40; 3.79
Processing Speed						
Motor Screening	Speed	482	0.03	0.05	0.00	0.01
			0.08;0.14	0.07; 0.16	0.12; 0.12	0.11; 0.13
Reaction Response	speed	458	0.02	0.02	0.07	0.06
			0.31; 0.23	0.32; 0.28	0.39; 0.25	0.39; 0.26
Attention						
Rapid Visual Info Processing	Speed	472	0.01	0.01	0.16	0.16
			0.21; 0.19	0.21; 0.20	0.38; 0.06	0.38; 0.06
	accuracy	473	0.00	0.00	0.02	0.02
			0.03; 0.03	0.03; 0.03	0.06; 0.01	0.06; 0.01
Multi-tasking	Speed	474	0.02	0.02	0.03	0.02
			0.03;0.07	0.03;0.08	0.09; 0.04	0.08; 0.04
	accuracy	477	1.86	1.68	4.05	4.07
			7.03; 3.33	7.00; 3.63	9.81; 1.73	9.91; 1.78
Memory						
Paired Associates Learning	accuracy	462	0.73	0.78	0.32	0.38
			1.83; 0.38	1.91; 0.35	1.54; 0.92	1.62; 0.87
Spatial Working Memory	accuracy	476	0.31	0.36	0.76	0.73
			1.17; 1.78	1.15; 1.88	2.41; 0.88	2.39; 0.94
	strategy	477	0.26	0.24	0.16	0.16
			0.65; 0.13	0.63; 0.15	0.27; 0.59	0.27; 0.60

Adjusted for age, grade, sex, area, head injury, smoke, alcohol, drugs, farm residence, mobile phone problematic use score, mobile phone ownership.

*Adjusted+ = Adjusted + mother employment, mother education, home language, household size, government grant, repeated grade, preschool, learner support. Data presented as the Beta from linear regression models.

Ref = low exposure "never pick crops"), moderate exposure ="pick crops with PPE", high exposure ="pick crops without PPE".

assessment. However, there is uncertainty to what extent such measures reflect long term exposure as biological half life time is short for the majority of metabolites. Thus, our activity related exposure surrogates may represent a more stable measure for long term pesticide exposure. We asked about recent and long-term pesticide exposure related activities and found very high agreement, indicating that such activities represent a long-term behavior. However, we could not validate, to what extent hypothetical exposure proxies correspond with actual exposure. For instance, we expected that children reporting washing fruit and wearing PPE during crop picking may have low pesticide exposure. However, we could not find consistent exposure–response patterns in relation to these protective measures. A possible explanation might be reverse causality that applying protective measures is correlated with higher likelihood of pesticide contact, in general. Thus, overall exposure for children taking protection measures may not be as low as anticipated. In addition, we cannot account for bias in self-reports and the quality (re-used or new) and compliant use of PPE provided to the children from the type of exposure data we have used in this analysis. Another challenge for interpretation is the fact that the same behavior may result in exposure to different types of pesticides,

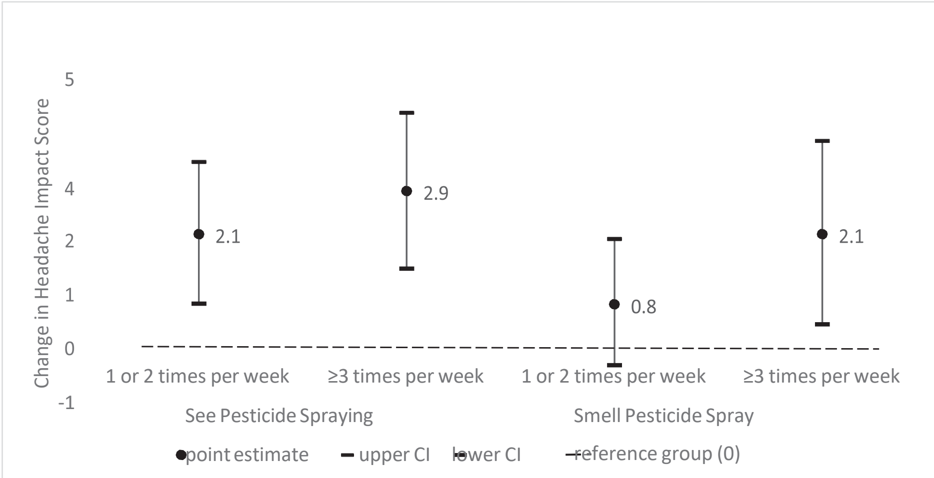

Fig. 3. Change in headache impact score in the full sample relation to the gradient of exposure to seeing and smelling pesticide spray.

depending on the area, the type of agriculture or the season. Various pesticides may have different neurocognitive effects, which may explain why we could not identify, except for headache, consistent exposur- e–response associations for any of the cognitive tests. The complex mixtures of pesticide exposure situation has been demonstrated in a recent measurement study in rivers of our three study areas (Curchod et al., 2020). A total of 53 pesticides were above the limit of detection, some of them in high concentrations. The majority of OPs include the neurotoxic ingredients atrazine, diazinon, chlorpyrifos and malathion, two of which, carbaryl and imidacloprid, are banned in the EU. Similar results were found in an analysis of 27 current-use pesticides in air at 20 sampling sites across Africa with six sites from the Western Cape (Fuh- rimann et al., 2020).

4.1. Strength and limitations

A strength of this study is the cognitive outcome assessment using standardized tests administered on a Tablet, which is in line with sug- gestions of clinicians to measure the neurotoxic effects of children, specifically in three domains: memory, executive functioning and attention (Vorhees et al., 2018; Carrillo et al., 2016). This approach is unlikely to create a bias with respect to the exposure assessment. Lim- itations of the study include the cross-sectional design, limiting con- clusions regarding causal inference of observed associations. The sample size of certain farm activities are relatively small and thus the power of the study is limited, which may be an explanation for the many non- significant results despite an overall indication of negative exposure impact. The study includes self-reported exposure measures and we have not validated how well these measures correspond to objective measures such as metabolites in urine or in hair samples. The latter have been found to be reliable measure of long-term exposure to pesticides amongst child workers employed in farming, and were suggested for an ongoing monitoring program for genotoxicity and consequent biological health effects (Vidi et al., 2017). The complexity of pesticide mixtures detected in the air and water sampling, and the different types of pes- ticides, depending on the area, the type of agriculture or the season will be considered in the next steps of the analysis with objective data to link these behaviors to specific pesticide groups. As in every observational study, confounding may also be of concern. For a subset of the cohort, we additionally adjusted for five socio-demographic variables derived from the guardian survey. However, this had little effect on the regres- sion coefficients (Table 3, Table 5 and Table S8), indicating that residual confounding is unlikely to play a major role in this analysis.

4.2. Implications

Literature on long-term pesticide exposure in school-aged children is still rare. A study examining the long-term cognitive effects in cumula- tive exposure between adolescent applicators and non-applicators, over three seasonal time-points, concluded that the deficits in neuro- behavioral performance was consistently observed amongst the high exposure group compared to the low exposure groups, even months after the application season (Rohlman et al., 2016). The specific cognitive deficits in executive functioning, memory and behavioral attention in this study (Rohlman et al., 2016), coincides with our findings, as well as three systematic reviews on the association of pesticides to neuro- development (González-Alzaga et al., 2014; Ross et al., 2012; Ntzani et al., 2013), including the effects in 6–9 year olds living in the vicinity of banana plantations, exposed to chlorpyrofis, mancozeb and pyre- throids (van Wendel de Joode et al., 2016). A study using the same CANTAB tool in OP self-poisoned patients coincides with impairment in the same sub-domains of attention (rapid visual processing) and mem- ory (paired associates learning and spatial working memory strategy) as our study participants who engage with eating and picking crops directly from the field (Dassanayake et al., 2020). In a study of mice, long-term low-dose exposure to malathion (an insecticide) was found to cause cognitive and spatial working memory impairment (dos Santos et al., 2016; van Wendel de Joode et al., 2016). A recent review concluded that low-level pesticide exposure of children may increase the risk to develop Attention Deficit Hyperactivity Disorder (ADHD) and autism (Roberts et al., 2019).

Based on our results and recent studies on pesticides and their burden of cardiovascular disease and respiratory health (Darçin and Darçin, 2017), a stricter control on management, storage, packaging and several processes after sales of pesticide is warranted. Given that these participants are not in occupation, a recommendation is to implement an educational program on pesticide related activities in schools and to learn from current interventions and their effectiveness (Griffith et al., 2019 May; Muñoz-Quezada et al., 2019; Rohlman et al., 2020 Dec). Given South Africa's history and socio-economic divide to the farm la- borers with short-term working contracts, future interventions should aim to reduce the health risks of these vulnerable populations including their children.

5. Conclusion

Our results are suggestive of long-term detrimental health effects on headaches and cognitive function amongst children in these agricultural communities engaged in pesticide-related farm and leisure activities, specifically eating crops off the field and picking crops from the field. Our findings are novel since this is one of the few studies to address specific activities associated with pesticide exposure in this specific age group. As a next step, longitudinal analysis with biomarkers are needed to validate these pesticide exposure proxies.

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Ethical approval

The ethical protocols for the study on pesticide exposure and reproductive health outcomes has been approved by the University of Cape Town's Human Research Ethics Committee (HREC reference number: 234/2009). An amendment was made to this protocol for the addition of neurobehavioral outcome and submitted for ethical clearance, which was approved on 24 May 2017 by the University of Cape Town's Human Research Ethics Committee (reference: 234/2009). The Swiss Tropical Pubic Health Institute Research Commission has ethically approved the proposal for the neurobehavior study in April 2017 (reference: EKNS 2017-01683). In addition, the Western Cape Education Department has provided approval and consent to conduct this study amongst the children who attend school in these study areas (reference: 20150629-846).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.106237.

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7. Supplementary Material

Association of activities related to pesticide exposure on headache severity and neurodevelopment of school-children in the rural agricultural farmlands of the Western Cape of South Africa

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Table S1: Overview of CANTAB test battery

	Cognitive domain	Test	Cognitive function	Outcome	Duration of test
1	Processing speed including visual motor integration	Reaction Response (RR)	Perception of visual stimuli, response to visual stimuli and execution of motor action	movement time, reaction time and response accuracy;	6 minutes
		Motor Screening (MS)	Sensorimotor or perceptual motor speed and comprehension difficulties	Time lapse between display to response; number of correct and incorrect responses	2 minutes
2	Memory including executive Functioning	Spatial Working Memory (SWM)	Manipulation of visuo-spatial information, executive demands of strategy (reasoning, decision making and behaviour), parts of short-term memory (holding) concerned with immediate conscious perceptual and linguistic processing	Visits, re-visits and searches for boxes	5 minutes
		Paired Associate Learning (PAL)	Visual memory and new learning, episodic memory (collection of past, personal experience that occurred at a particular time and place with associated emotions)	Incorrect selection, adjustment, problem solving and memory of selection	8 minutes
3	Attention	Multi-tasking (MTT)	Attentional set-shifting, cognitive flexibility and lateralization	Congruency and latency during change of instructions	8 minutes
		Rapid Visual Information Processing (RVP)	Sustained attention and continuous performance, impulse control or inhibition	Sensitivity to target and correct responses	7 minutes

Table S2: Demographic of the children enrolled in the cohort study in the Western Cape, South Africa between 2017 and 2019, stratified by gender and area.
**TBI –Traumatic Brain Injury*

	Gender		Chi2 *p*-value	Area 1	Area 2	Area 3	Chi2 *p*-value
	Male n (%)	Female n (%)		Grabouw n (%)	Piketberg n (%)	DeDoorn n (%)	
TOTAL n (%)	473 (47.2)	528 (52.7)		325 (32.5)	303 (30.3)	373 (37.2)	
Age categories 9-11 years	291 (61.5)	301 (57.0)	0.10	194 (59.7)	223 (73.6)	175 (46.9)	<0.01
12-14 years	203 (42.9)	153(29.0)		116 (35.7)	79 (26.1)	161 (43.2)	
15-16 years	29 (6.13)	24 (5.6)		15 (4.6)	1 (0.3)	37 (9.9)	
Grade categories 2^{nd}-3^{rd}	85 (18.0)	78 (14.8)	0.03	37 (11.4)	77 (25.4)	49 (13.1)	<0.01
4^{th}-6^{th}	322 (68.1)	345 (65.3)		235 (72.3)	210 (69.3)	222 (59.5)	
7^{th}-9^{th}	66 (14.0)	105 (20.0)		53 (16.3)	16 (5.3)	102 (27.3)	
Head Injury (ever)							
0 (none)	289 (61.1)	370 (70.1)	0.01	216 (66.5)	192 (63.4)	251 (67.3)	0.60
1 (fell&hit head)	120 (25.4)	110 (20.8)		78 (24.0)	71 (23.4)	81 (21.7)	
2 (potential TBI*)	64 (13.5)	48 (9.1)		31 (9.5)	40 (13.2)	41 (11.0)	
Smoke (ever) No	398 (84.1)	456 (86.4)	0.32	273 (84.0)	255 (84.2)	326 (87.4)	0.36
Yes	75 (15.9)	72 (13.6)		52 (16.0)	48 (15.8)	47 (12.6)	
Alcohol Use (ever) No	397 (83.9)	454 (86.0)	0.36	281 (86.4)	264 (87.1)	306 (82.0)	0.12
Yes	76 (16.1)	74 (14.0)		44 (13.5)	39 (12.9)	67 (18.0)	
Drug Use (ever) No	452 (95.6)	524 (99.2)	<0.01	317 (97.5)	294 (97.0)	365 (97.9)	0.80
Yes	21 (4.4)	4 (0.8)		8 (2.5)	9 (3.0)	8 (2.1)	
Indoor leisure activities							

Mobile Phone Use (current) No	318 (67.2)	365 (69.1)	0.52	138 (42.5)	240 (79.2)	305 (81.8)	<0.01
Yes	155 (32.8)	163 (30.9)		187 (57.5)	63 (20.8)	68 (18.2)	
Electronic Media Use (current)							
No	250 (52.9)	290 (54.9)	0.51	100 (30.8)	167 (55.1)	273 (73.2)	<0.01
Yes	223 (47.2)	238 (45.1)		225 (69.2)	136 (44.9)	100 (26.8)	

TableS3: Characteristics and activities related to pesticide exposure

Survey Question Long-term: "Have you ever helped with…" Short-term: "In the last 7 days, did you help with	Total n (%)	Sub-cohort Total n (%)
Total n (%)	1001(100)	482 (100)
Farm resident	465 (46.4)	179 (37)
Any family member working on a farm	660 (65.9)	308 (64)
Parent works on a farm	473 (47.3)	215 (45)
Ever seen pesticide spraying activities	802 (80.2)	381 (79)
If yes, which spraying activities have you seen:		
Aeroplane (past 7 days)		
One day a week	63 (6.3)	30 (6)
Two days a week	46 (4.6)	26 (5)
Three or more days a week	85 (8.5)	43 (9)
Tractor (past 7 days)		
One day a week	141 (14.1)	67 (14)
Two days a week	118 (11.8)	54 (11)
Three or more days a week	196 (19.6)	95 (20)
Knapsack (past 7 days)		
One day a week	74 (7.4)	41 (9)
Two days a week	43 (4.3)	18 (4)
Three or more days a week	57 (5.7)	26 (5)
Smell pesticide spraying	519 (51.9)	228 (47)
Farm activities (ever)	474 (47.4)	225 (47)
Picking fruits	246 (24.6)	116 (24)
Wore PPE when picking	142 (14.2)	69 (14)
Spraying, mixing, loading	57 (5.7)	34 (7)
Cleaning farm equipment	223 (22.3)	105 (22)
Pesticide storage	206 (20.6)	101 (21)
Burning pesticide containers	56 (5.6)	29 (6)
Leisure Activities (ever)		
Play, swim or bathe in water	494 (49.4)	230 (48)
Eat crops directly from orchard	515 (51.5)	273 (57)
Always wash fruit before eating	566 (56.6)	266 (55)

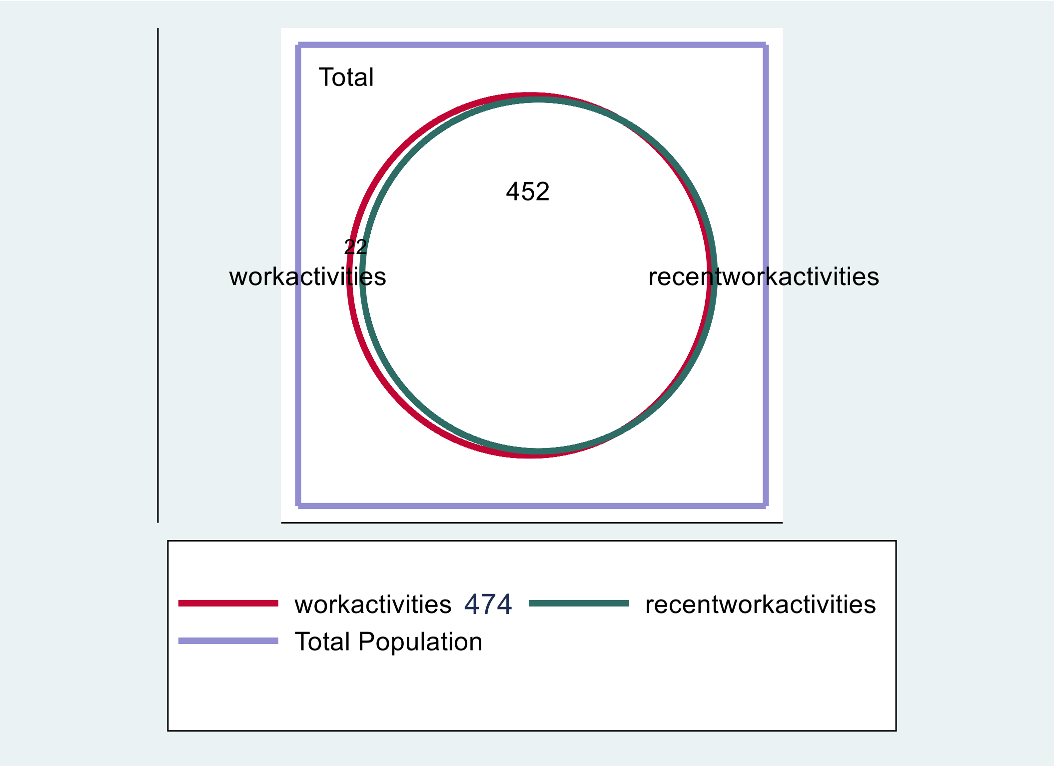


Figure S1: The proportional overlap between ever and last seven days reported farm activities

Table S4: Characteristics and activities related to pesticide exposure stratified by gender and area

	Gender		Chi2	Area 1	Area 2	Area 3	Chi2
	Male n (%)	Female n (%)	*p*-value	Grabouw n (%)	Piketberg n (%)	DeDoorn n (%)	*p*-value
TOTAL n (%)	**473 (47.2)**	**528 (52.7)**		**325 (32.5)**	**303 (30.3)**	**373 (37.2)**	
Farm resident	223 (47.2)	242 (45.8)	0.70	202 (62.2)	121 (39.9)	142 (38.1)	<0.01
Family member works on a farm	318 (67.2)	342 (64.8)	0.41	199 (61.2)	180 (59.4)	281 (75.3)	<0.01
Parent works on a farm	232 (49.0)	241 (45.6)	0.30	147 (45.2)	108 (35.6)	218 (58.5)	<0.01
Ever seen pesticide spraying activities	398 (84.1)	404 (76.5)	<0.01	278 (85.5)	233 (76.9)	291 (79.6)	0.01
If yes, which spraying activities have you seen:			<0.01				0.08
Aeroplane (past 7 days)							
One day a week	28 (5.9)	35 (6.6)		21 (6.5)	27 (8.9)	15 (4.0)	
Two days a week	26 (5.5)	20 (3.8)		11 (3.4)	13 (4.3)	22 (5.9)	
Three or more days a week	60 (12.7)	25 (4.7)		22 (6.8)	29 (9.6)	34 (9.1)	
Tractor (past 7 days)							
One day a week	61 (12.9)	80 (15.2)	0.09	49 (15.1)	40 (13.2)	52 (13.9)	0.70
Two days a week	62 (13.1)	56 (10.6)		34 (10.5)	43 (14.2)	41 (11.0)	
Three or more days a week	105 (22.2)	91 (17.2)		60 (18.5)	64 (21.1)	72 (19.3)	
Knapsack (past 7 days)							
One day a week	29 (6.1)	45 (18.5)	0.03	25 (7.7)	18 (5.6)	31 (8.3)	0.90
Two days a week	28 (5.9)	15 (2.8)		13 (4.0)	15 (5.0)	15 (4.0)	
Three or more days a week	31 (6.6)	26 (4.9)		17 (5.2)	20 (6.6)	20 (5.4)	
Smell pesticide spraying	254 (53.7)	265 (50.2)	0.30	211 (64.9)	145 (47.9)	163 (43.7)	<0.01
Farm activities (ever)	252 (53.3)	222 (42.1)	<0.01	138 (42.5)	136 (44.9)	200 (53.6)	<0.00
Picking fruits	150 (31.7)	96 (18.2)	<0.01	59 (18.2)	72 (23.8)	115 (30.8)	<0.01
Wore PPE when picking	93 (19.7)	49 (9.3)	<0.01	38 (11.7)	36 (11.9)	68 (18.2)	0.02

Spraying, mixing, loading	35 (7.4)	22 (4.2)	**0.03**	16 (4.9)	17 (5.6)	24 (6.4)	0.70
Cleaning farm equipment	127 (26.9)	96 (18.2)	**<0.01**	63 (19.4)	63 (20.8)	97 (26.0)	0.08
Pesticide storage	100 (21.1)	106 (20.1)	0.70	65 (20)	49 (16.2)	92 (24.7)	**0.02**
Burning pesticide containers	38 (8.0)	18 (3.4)	**<0.01**	17 (5.2)	19 (6.3)	20 (5.4)	0.83
Leisure Activities (ever) Play, swim or bathe in water	264 (55.8)	230 (43.6)	**<0.01**	169 (52.0)	128 (42.2)	197 (52.8)	**0.01**
Eat crops directly from orchard	253 (53.5)	262 (49.6)	0.22	137 (42.2)	121 (40.0)	257 (68.9)	**<0.01**
Always wash fruit before eating	259 (54.8)	307 (58.1)	0.44	189 (58.2)	209 (69.0)	168 (45.0)	**<0.01**

Figure S2 Proportional overlap between the pesticide-related exposure proxies

Table S5: Linear regression analysis results from the full sample: changes in headache score and six cognitive performance outcome scores in relation to eating crops, combined with frequency of washing fruit

				Eating and washing fruit					
	Domain		Ref(n=289)	Moderate Exposure (n=648)			High Exposure (n=64)		
		n		Beta (β)	CI	P-value	Beta (β)	CI	P-value
Health Symptom									
Headaches		999		0.34	-0.87; 1.56	0.58	**-2.92**	**-5.26;-0.58**	**0.02**
Processing Speed									
Motor Screening	speed	997	0	-0.19	-0.08; 0.04	0.52	-0.08	-0.20; 0.03	0.15
Reaction Response	speed	961	0	**-0.15**	**-0.31; 0.00**	**0.05**	-0.11	-0.40; 0.19	0.48
Attention									
Rapid Visual Processing	speed	981	0	0.02	-0.08; 0.13	0.66	**0.27**	**0.06; 0.47**	**0.01**
	accuracy	984	0	-0.01	-0.02; 0.01	0.36	-0.03	-0.06; 0.00	0.09
Multi-tasking	speed	986	0	0.00	-0.03; 0.03	0.90	0.00	-0.06; 0.06	0.95
	accuracy	994	0	1.01	-1.64; 3.76	0.44	**-5.32**	**-10.53;-0.12**	**0.05**
Memory									
Paired Associates Learning	accuracy	968	0	-0.53	-1.08; 0.03	0.06	-0.32	-1.41; 0.77	0.57
Spatial Working Memory	accuracy	990	0	-0.28	-1.06; 0.51	0.49	-0.37	-1.87; 1.14	0.63
	accuracy	990	0	0.05	-0.16; 0.26	0.64	0.19	-0.20; 0.59	0.34

**Adjusted for age, grade, sex, area, head injury, smoke, alcohol, drugs, farm residence, mobile phone problematic use score, mobile phone ownership*

Ref= low exposure "never eat fruit" and "always wash fruit"; moderate exposure= "eat crops from the field and sometimes or always washing fruit"; high exposure= "eat fruit and never or rarely washing fruit"

Table S6: Linear regression analysis results from the subgroup with and without adjustment for socio-demographic factors: changes in headache score and six cognitive performance outcome scores in relation to eating crops, combined with frequency of washing fruit.

				Eating and washing fruit			
	Domain		Ref(n=116)	Moderate Exposure (n=330)		High Exposure (n=36)	
		n		Beta (β) CI Adjusted	Beta (β) CI Adjusted+*	Beta (β) CI Adjusted	Beta (β) CI Adjusted+*
Health Symptom							
Headaches		481	0	0.96 -0.87; 2.81	**-4.27 -7.52; -1.02**	1.05 -0.83; 2.93	**-4.21 -7.52; -0.90**
Processing Speed							
Motor Screening	speed	482	0	0.01 -0.08; 0.09	0.02 -0.07; 0.11	-0.07 -0.22; 0.09	-0.03 -0.19; 0.13
Reaction Response	speed	458	0	**-0.25 -0.49; -0.02**	**-0.25 -0.49; -0.01**	-0.17 -0.58; 0.25	-0.16 -0.58; 0.27
Attention							
Rapid Visual Processing	speed	472	0	0.06 -0.10; 0.22	0.07 -0.09; 0.23	0.21 -0.07; 0.49	0.18 -0.10; 0.47
	accuracy	473	0	-0.02 -0.04; 0.01	-0.02 -0.04; 0.01	-0.03 -0.07; 0.01	-0.03 -0.07; 0.02
Multi-tasking	speed	474	0	0.00 -0.03; 0.03	0.01 -0.03; 0.06	0.01 -0.07; 0.09	0.02 -0.06; 0.10
	accuracy	477	0	-0.07 -4.26; 4.12	-0.59 -4.86; 3.67	**-7.77 -15.13;-0.40**	**-8.14 -15.62; -0.66**
Memory							
Paired Associates Learning	accuracy	462	0	-0.62 -1.49; 0.25	-0.62 -1.52; 0.27	-0.24 -1.83; 1.35	-0.13 -1.75; 1.49
Spatial Working Memory	accuracy	476	0	-0.36 -1.56; 0.83	-0.39 -1.62; 0.82	-1.30 -3.41; 0.80	-1.34 -3.48; 0.80
	accuracy	477	0	-0.05 -0.36; 0.27	0.01 -0.31; 0.33	0.12 -0.43; 0.67	0.12 -0.43; 0.68

**Adjusted for age, grade, sex, area, head injury, smoke, alcohol, drugs, farm residence, mobile phone problematic use score, mobile phone ownership*

**Adjusted+ = Adjusted+mother employment, mother education, home language, household size, government grant, repeated grade*, preschool, learner support

Ref= low exposure "never eat fruit" and "always wash fruit"; moderate exposure= "eat crops from the field and sometimes or always washing fruit"; high exposure= "eat fruit and never or rarely washing fruit"

Table S7: Linear regression analysis results from the full sample: changes in symptom and six cognitive performance outcome scores in relation to four pesticide-related exposures between those who engage in these behaviors and those who do not

			Cleaning (n=223)			Storing (n=206)			Burning (n=56)			Spray,Mix,Loading (n=57)		
	Score	n	Beta (β)	95% CI	P-value	Beta (β)	95%CI	P-value	Beta (β)	95% CI	P-value	Beta (β)	95% CI	P-value
Health Symptom														
Headaches	Total	999	0.92	-0.38; 2.22	0.17	**1.46**	**0.12; 2.81**	**0.03**	0.46	-1.81; 2.73	0.69	-0.12	-2.37; 2.13	0.92
Processing Speed														
Motor Screening	Speed	997	0.02	-0.05; 0.08	0.58	0.05	-0.02; 0.11	0.16	0.03	-0.07; 0.14	0.53	-0.06	-0.17; 0.05	0.26
Reaction Response	Speed	961	0.00	-0.17; 0.16	0.99	-0.06	-0.23; 0.10	0.46	-0.02	-0.31; 0.26	0.88	-0.18	-0.46; 0.11	0.22
Attention														
Rapid Visual Processing	Speed	981	-0.08	-0.20; 0.03	0.16	0.01	-0.10; 0.13	0.82	0.01	-0.19; 0.20	0.96	0.04	-0.16; 0.24	0.69
	Accuracy	984	0.00	-0.01; 0.02	0.76	0.00	-0.02; 0.02	0.93	0.01	-0.02; 0.04	0.66	-0.02	-0.05; 0.01	0.22
Multi-tasking	Speed	986	0.01	-0.02; 0.04	0.42	0.00	-0.03; 0.03	0.87	-0.01	-0.06; 0.04	0.73	0.02	-0.03; 0.08	0.38
	Accuracy	994	**-2.30**	**-5.83;-0.16**	**0.04**	-0.51	-3.44; 2.41	0.73	2.98	-2.08; 8.06	0.25	4.88	-0.12; 9.89	0.06
Memory														
Paired Associates Learning	Accuracy	969	-0.41	-1.01; 0.20	0.19	-0.43	-1.05; 0.18	0.17	0.53	-0.52; 1.58	0.33	-0.05	-1.09; 1.00	0.93
Spatial Working Memory	Accuracy	991	0.59	-0.25; 1.43	0.17	-0.27	-1.13; 0.59	0.54	-1.10	-2.57; 0.36	0.14	0.28	-1.16; 1.73	0.70
	Strategy	991	0.01	-0.21; 0.23	0.93	0.03	-0.19; 0.26	0.77	-0.30	-0.68; 0.10	0.13	-0.05	-0.04; 0.34	0.81

**Adjusted for age, grade, sex, area, head injury, smoke, alcohol, drugs, farm residence, mobile phone problematic use score, mobile phone ownership*

Table S8: Linear regression analysis results from the subgroup with and without adjustment for socio-demographic factors: changes in headache score and six cognitive performance outcome scores in relation to four pesticide-related exposures between those who engage in these behaviors and those who do not

			Cleaning (n=105)		Storing (n=101)		Burning (n=29)		Spray,Mix,Loading (n=34)	
	Score	n	Beta (β) 95% CI Adjusted	Beta (β) 95% CI Adjusted+*	Beta (β) 95%CI Adjusted	Beta (β) 95% CI Adjusted+*	Beta (β) 95% CI Adjusted	Beta (β) 95% CI Adjusted+*	Beta (β) 95% CI Adjusted	Beta (β) 95% CI Adjusted+*
Health Symptom										
Headaches	Total	481	0.14 -1.81; 2.08	0.17 -1.80; 2.15	1.05 -0.91; 3.00	1.21 -0.77; 3.20	-0.05 -3.31; 3.20	0.07 -3.29; 3.32	1.08 -1.88; 4.05	1.10 -1.92; 4.12
Processing Speed										
Motor Screening	Speed	482	0.05 -0.05; 0.14	0.03 -0.06; 0.13	**0.09** **0.00; 0.19**	0.09 0.00; 0.19	0.00 -1.16; 0.15	0.01 -1.14; 0.17	-0.06 -0.20; 0.09	-0.05 -0.19; 0.09
Reaction Response	Speed	458	-0.18 -0.42; 0.07	-0.18 -0.43; 0.07	-0.22 -0.46; 0.03	-0.23 -0.47; 0.02	-0.20 -0.61; 0.21	-0.21 -0.63; 0.21	-0.13 -0.50; 0.25	-0.17 -0.55; 0.21
Attention										
Rapid Visual Processing	Speed	472	0.01 -0.15; 0.18	0.02 -0.14; 0.20	0.15 -0.01; 0.32	0.17 0.00; 0.34	0.22 -0.06; 0.50	0.23 -0.04; 0.52	0.09 -0.17; 0.35	0.08 -0.18; 0.33
	Accuracy	473	0.00 -0.02; 0.03	0.00 -0.03; 0.03	0.00 -0.03; 0.02	-0.01 -0.03; 0.02	0.01 -0.04; 0.05	0.01 -0.03; 0.05	**-0.04** **-0.08; -0.01**	**-0.05** **-0.09; -0.01**
Multi-tasking	Speed	474	0.00 -0.05; 0.04	0.00 -0.05; 0.04	-0.01 -0.06; 0.03	-0.02 -0.06; 0.03	0.02 -0.06; 0.10	0.02 -0.06; 0.09	0.05 -0.02; 0.12	0.04 -0.02; 0.12
	Accuracy	477	-3.64 -8.01;0.72	-3.90 -8.31; 0.52	-1.11 -5.51; 3.29	-1.00 -5.45; 3.47	4.06; -3.24; 11.36	4.33; -3.06; 11.73	7.17 0.55; 13.81	7.29 0.55; 14.03
Memory										
Paired Associates Learning	Accuracy	462	0.44 -0.47; 1.37	0.41 -0.53; 1.34	-0.42 -1.34; 0.50	-0.49 -1.42; 0.44	0.88 -0.69; 2.50	0.89 -0.70; 2.49	-0.27 -1.69; 1.16	-0.33 -1.79; 1.12
Spatial Working Memory	Accuracy	476	0.25 -0.10; 1.50	0.10 -1.17; 1.36	-0.70 -1.95; 0.55	-0.72 -1.99; 0.55	-0.01 -2.12; 2.11	0.07 -2.08; 2.21	0.25 -1.68; 2.17	0.10 -1.85; 2.06
	Strategy	477	0.09 -0.24; 0.42	0.11 -0.22; 0.44	0.01 -0.32; 0.34	0.04 -0.29; 0.37	0.60 0.05; 1.16	0.63 0.07; 1.19	0.05 -0.46; 0.55	0.06 -0.45; 0.56

Adjusted for age, grade, sex, area, head injury, smoke, alcohol, drugs, farm residence, mobile phone problematic use score, mobile phone ownership
**Adjusted+ = Adjusted+mother employment, mother education, home language, household size, government grant, repeated grade*, preschool, learner support

Table S9: Linear regression analysis results from the full sample, stratified by age: changes in headache score and six cognitive performance outcome scores in relation to three pesticide-related exposures between those who answered yes to these behaviors and those who answered no

Adjusted for age, grade, sex, area, head injury, smoke, alcohol, drugs, farm residence, mobile phone problematic use score, mobile phone ownership

			Work activities (n=474)		Eating crops (n=515)		Leisure activities (n=494)	
			(n=273)	(n=201)	(n=282)	(n=233)	(n=269)	(n=225)
	Score	n	Beta (β) (95% CI) Age (9.0-11.12)	Beta (β) (95% CI) Age (12.0-16.12)	Beta (β) (95% CI) Age (9.0-11.12)	Beta (β) (95% CI) Age (12.0-16.12)	Beta (β) (95% CI) Age (9.0-11.12)	Beta (β) (95% CI) Age (12.0-16.12)
Symptom								
Headaches (n=591; 408)	Total	999	1.91 (0.42; 3.42)	1.90 (0.15; 3.65)	2.15 (0.69; 3.61)	0.55 (-1.22; 2.32)	1.56 (0.14; 2.98)	0.66 (-1.02; 2.34)
Processing Speed								
Motor Screening (n=588; 409)	Speed (seconds)	997	0.05 (-0.02; 0.12)	0.02 (-0.07; 0.11)	-0.04 (-0.11; 0.03)	-0.11 (-0.20; -0.02)	0.01 (-0.06; 0.08)	-0.02 (-0.10; 0.06)
Reaction Response (n=573; 388)	Speed	961	-0.16 (-0.34; 0.03)	-0.05 (-0.28; 0.18)	-0.04 (-0.22; 0.14)	-0.35 (-0.58; -0.12)	-0.10 (-0.25; 0.09)	-0.08 (-0.31; 0.14)
Attention								
Rapid Visual Processing (n=576; 405)	Speed	981	-0.05 (-0.18; 0.80)	-0.02 (-0.17; 0.13)	0.09 (-0.04; 0.22)	-0.17 (-0.32; -0.19)	-0.01 (-0.13; 0.11)	-0.07 (-0.21; 0.08)
Multi-tasking (n=581; 405)	Speed	986	0.01 (-0.02; 0.05)	0.01 (-0.04; 0.05)	0.02 (-0.02; 0.05)	-0.04 (-0.09; 0.00)	-0.01 (-0.04; 0.02)	-0.02 (-0.06; 0.02)
Memory								
Paired Associates Learning (n=566; 403)	Accuracy (hits)	869	-0.32 (-1.00; 0.37)	-0.65 (-1.46; 0.17)	-0.81 (-1.48; -0.14)	0.13 (-0.69; 0.96)	-0.19 (-0.84; 0.47)	-0.30 (-1.08; 0.48)
Spatial Working Memory (n=583; 408)	Strategy	991	-0.18 (-0.44; 0.07)	0.15 (-0.15; 0.45)	-0.10 (-0.35; 0.14)	0.13 (-0.18; 0.43)	-0.17 (-0.41; 0.07)	-0.15 (-0.43; 0.14)

Table S10: Linear regression analysis results from the full sample, stratified by age: changes in headache score and six cognitive performance outcome scores in relation to two pesticide-related exposures between those who answered yes to these behaviors and those who answered no, combined with protective factors

			Eat and wash fruit (n=474)		Picking and wearing PPE (n=515)	
	Score	n	Beta (β) (95% CI) Age (9.0-11.12) n=591	Beta (β) (95% CI) Age (12.0-16.12) n=408	Beta (β) (95% CI) Age (9.0-11.12) n=591	Beta (β) (95% CI) Age (12.0-16.12) n=408
Symptom						
Headaches	Total	999				
low exposure			ref	ref	ref	ref
moderate exposure			0.54 (-1.00; 2.07)	0.00 (-2.02; 2.01)	**2.86 (0.84; 4.87)**	2.09 (-0.38; 4.55)
high exposure			-1.32 (-4.46; 1.82)	**-4.98 (-8.55; -1.42)**	1.18 (-1.33; 3.68)	2.29 (-0.14; 4.72)
Processing Speed						
Motor Screening	Speed (seconds)	997				
low exposure			ref	ref	ref	ref
moderate exposure			0.00 (-0.08; 0.07)	-0.05 (-0.15; 0.05)	0.09 (0.00; 0.19)	-0.03 (0.16; 0.09)
high exposure			-0.07 (-0.22; 0.07)	-0.11 (-0.29; 0.07)	0.01 (-0.10; 0.13)	-0.10 (-0.22; 0.02)
Reaction Response	Speed	961				
low exposure			ref	ref	ref	ref
moderate exposure			-0.03 (-0.21; 0.16)	**-0.41 (-0.67; 0.14)**	0.07 (-0.18; 0.32)	-0.11 (-0.44; 0.22)
high exposure			0.02 (-0.36; 0.40)	-0.40 (-0.86; 0.07)	-0.14 (-0.45; 0.16)	-0.23 (-0.55; 0.08)
Attention						
Rapid Visual Processing	Speed	981				
low exposure			ref	ref	ref	ref
moderate exposure			0.08 (-0.05; 0.22)	-0.10 (-0.28; 0.07)	-0.09 (-0.27; 0.08)	-0.15 (-0.36; 0.06)
high exposure			**0.47 (0.21; 0.74)**	-0.08 (-0.39; 0.22)	**0.29 (0.71; 0.51)**	**-0.26 (-0.47; -0.05)**
Multi-tasking	Speed	986				
low exposure			ref	ref	ref	ref
moderate exposure			0.01 (-0.03; 0.05)	-0.02 (-0.07; 0.03)	0.05 (-0.03; 0.05)	0.03 (-0.03; 0.09)
high exposure			0.01 (-0.07; 0.09)	-0.02 (-0.11; 0.07)	0.03 (-0.03; 0.09)	-0.04 (-0.10; 0.03)
Memory						
Paired Associates Learning	Accuracy (hits)	869				
low exposure			ref	ref	ref	ref
moderate exposure			**-0.88 (-1.58; -0.18)**	0.12 (-0.82; 1.07)	**-1.21 (-2.13; -0.28)**	-0.33 (-1.48; 0.82)
high exposure			-0.84 (-2.28; 0.60)	0.44 (-1.31; 2.19)	0.22 (-0.91; 1.35)	-0.91 (-2.05; 0.24)
Spatial Working Memory	Strategy	991				
low exposure			ref	ref	ref	ref
moderate exposure			-0.05 (-0.31; 0.21)	0.15 (-0.20; 0.49)	**-0.43 (-0.77; -0.09)**	-0.07 (-0.49; 0.35)
high exposure			0.19 (-0.34; 0.72)	0.21 (-0.40; 0.83)	-0.03 (-0.46; 0.39)	0.27 (-0.14; 0.69)

Eat and wash fruit: low exposure ("never eat fruit" and "always wash fruit"); moderate exposure ("eat crops from the field and sometimes or always washing fruit"); high exposure ("eat fruit and never or rarely washing fruit"); Pick and wear PPE: low exposure ("never pick crops"), moderate exposure ("pick crops with PPE"), high exposure ("pick crops without PPE")

Chapter 6

6. Discussion

The Child Health Agricultural Cohort Study South Africa (CapSA) was conducted under the Swiss South African Joint Research Programme (SSAJRP) between the Swiss Tropical Public Health Institute (Swiss TPH) and the University of Cape Town's SARChI in Global Environmental Health. The thesis contributes to the Sustainable Development Goal (SDG) three, "to ensure healthy lives and promote well-being for all at all ages", the key activity area eight of Swiss TPH, "Health in Human-Environmental Systems: studying the impact of environmental factors on human health" and toward identifying hazardous neurotoxic pathways for the HIA and continued research under CapSA.

This study hypothesized that children reporting environmental-related exposure behaviours relating to e-media and agricultural pesticides will have lower neurocognitive outcome scores and higher health symptoms than children who do not engage in these exposure-related behaviours. We observe preliminary findings of an association in support of our hypothesis; significant lower neurocognitive performance scores and worse health symptoms were observed among learners who reported high problematic e-media use and those engaging in pesticide-related behaviours, specific to eating and picking crops from the nearby field, vineyard or orchard, and storing pesticide containers. This chapter will discuss the main findings of the thesis in each chapter, its relevance, challenges (strengths and weaknesses), recommendations and the way forward.

6.1 Methods and contribution of this thesis

The protocol paper in this thesis describes the CapSA study aims and objectives, design, methodology, research team, and emphasizes its novelty. The CapSA study was designed to represent the highest precision of data in epidemiology exposure and health assessment, including a variation of biological (blood, hair, urine samples, anthropometric measurements), environmental (air, water and soil samples), and health measurements at different time points, across varying seasons, and over three years. To date, the team has recruited 1,001 participants and collected baseline data on health outcomes of CANTAB, HRQOL, HIT-6, MPPUS-10 and participant questionnaires on all 1,001 learner participants, and 600 at the follow-up. Urine samples were collected but have not yet been analysed at three time points illustrated below in 2018. The guardian survey was collected in 2019, with 482 completed to date. The challenges of collecting data included logistical constraints; difficulty to reach parents working in the field for long hours of the day; restrictions by the education department to only test children during school hours outside of their examination months. Additionally, budget constraints relating to the fieldworker team and laboratory costs for storing and analysing the biological samples have been restrictive in the data collection process. Furthermore, GPS coordinates were difficult to capture via ODK on mobile phones, due to limited connectivity in certain rural areas.

These difficulties have delayed the availability of follow-up data for this thesis. The Masters in Public Health graduate student, first author of Chapter 5, will begin her PhD on the longitudinal analysis of this thesis' objectives, including follow-up data and biomarkers. Environmental water and air samples have been captured at different time points over each year, analysed and published. [119]

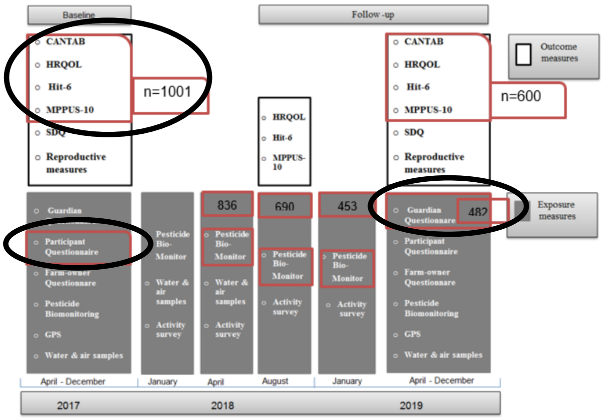


Figure 1 Diagram illustrating the data collection exposure and health outcome tools and timeline in CapSA, 2017-2019[74]

This is the first PhD of the CapSA study from which available baseline data on the full cohort was used, in parallel with the timeline of this thesis between 2016 and 2020. Participant survey data and four health outcomes including standardized health assessment tools collected in 2017 for 1,001 participants and the 482 guardian survey with socio-demographic data and maternal alcohol consumption questions collected in 2019 were used in this thesis. This thesis carries a large power intending to explore patterns of association with different physical and lifestyle environmental exposures and unpack sources of bias and confounding as the first steps toward investigating causation in CaPSA. The analysis will be complimented in future analyses with follow-up data, repeated measures over varying seasons, integrating biological and environmental sampling to account for individual exposure variation, in the next steps of CapSA. Scientists conclude that "establishing a fact or proof of causality is indeed a rigorous, perpetual process to gain the evidence with limited uncertainty, the harm may have occurred, and thus all preliminary processes leading toward the process of causality are crucial to gaining this scientific proof". [25]

To acknowledge the complexity of multi-influential factors on neurobehaviour of children, as explained in the introduction, with additional underlying social-economic, political and cultural determinants in a rural disadvantaged setting, the illustration in Figure 2 will be referenced to distinguish each role player in our chapters. [7 6]

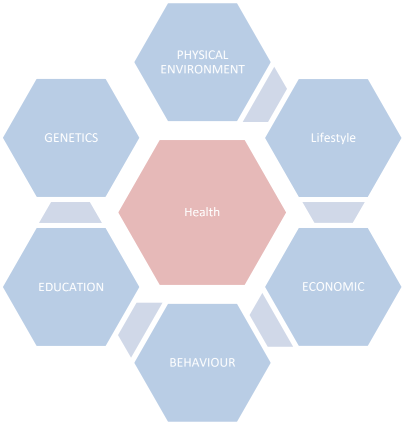


Figure 2 The multi-influential factors which play a role in health

6.1.1 Research exposure assessment strategy

Chapter three's findings confirm that past and present leisure and work pesticide exposure related behaviours overlap, indicating long-term chronic exposure.

To identify these potentially small/hidden effects in relation to the health outcomes (Figure 4), we explored the association by categorizing exposure groups in chapters three and five, despite the potential for errors which may have potentially occurred due to lowered power in small exposure groups. Every measured variable in an epidemiological study can only be considered as a surrogate or proxy for some more appropriate measures of the underlying phenomenon. A proxy is thus an indirect measure of exposure.

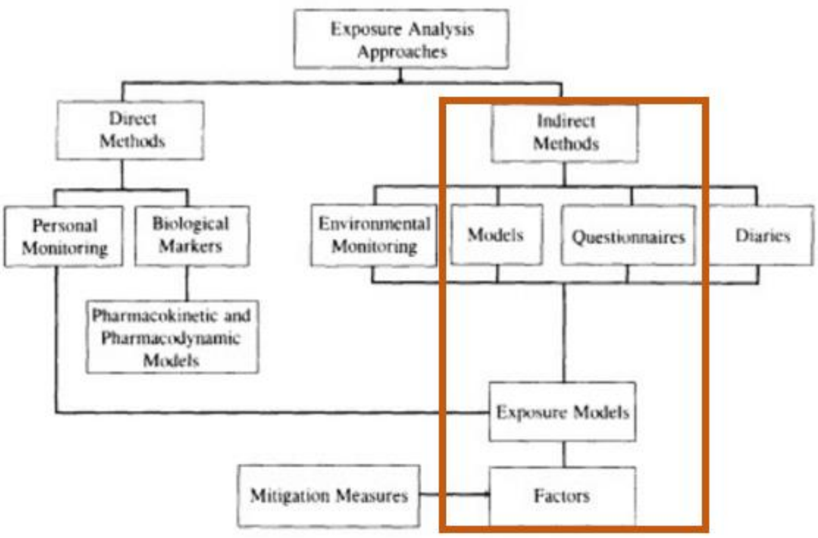
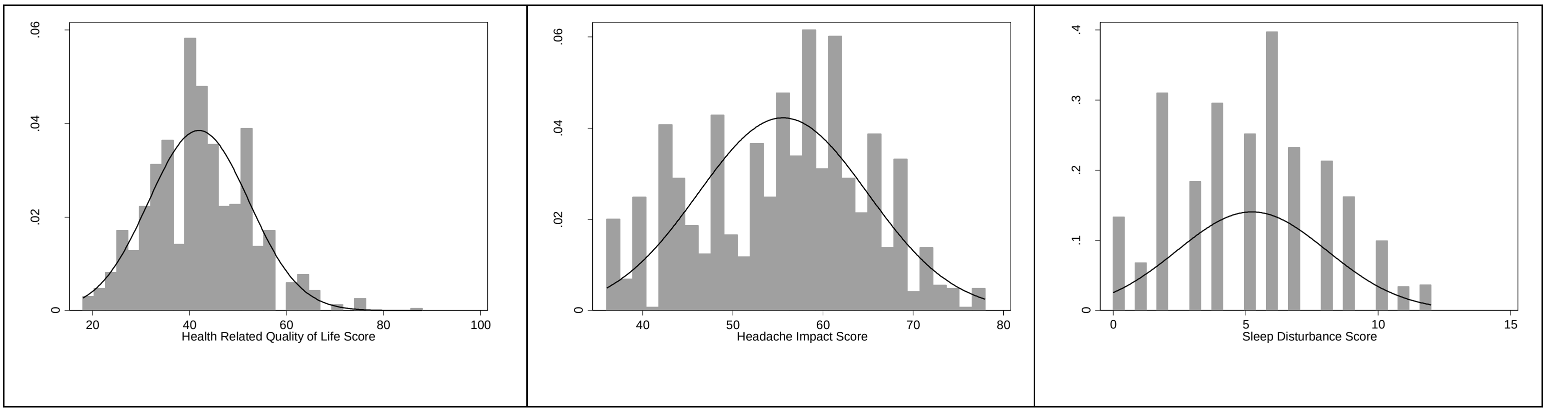


Figure 3 Possible approaches for exposure assessment [120]

An indirect method of exposure assessment with survey data and cognitive assessment, as outlined in Figure 3 was the approach used in this thesis to explore associations to the health outcomes illustrated in Figure 4 and six neurocognitive scores, using linear regression models to observe the association patterns.



Figures 4 The distribution patterns for each health outcome: HRQoL, headache, and sleep disturbance score

6.2 E-media and neurobehaviour

6.2.1 The association of lifestyle and behavioural factors on health and cognitive symptoms of children in rural South Africa

One-third of the cohort engages in mobile phone and e-media use. Through the exposure-response relationship in our analysis, distinguishing high and low exposure groups as illustrated in Figure 5, we could identify chronic effects in relation to the three health outcomes in Figure 4. The red confidence interval bar in the graphs represent the health effects in relation to the high exposure groups of average calls per day (≥6minutes a day->1 hour/day), night-time mobile phone awakenings (≥1 time/week up to 7 times/week), and mobile phone addiction (36-91 score) respectively, compared to the moderate exposure groups in blue and the reference group (non-users of mobile phones and e-media on the 0 lines. No exposure-response pattern was noted for total screen time.

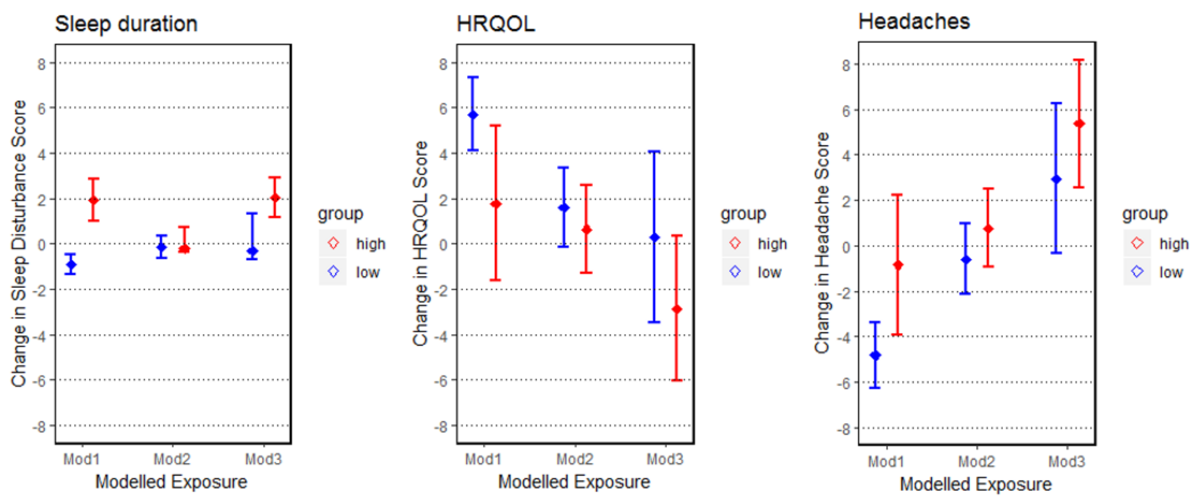


Figure 5 Change in health effects after adjusting for mobile phone in all exposure and health outcome models

Since HRQOL was positively associated across all four exposure models of e-media, we learnt that SES in this chapter was a backdoor path, which had to be adjusted to identify the true estimate of adverse health effects from problematic mobile phone use. Our analysis confirmed that mobile phone ownership is a proxy for a better lifestyle, and through adjusting we account for the underlying influential factors in a rural context, unmasking internationally comparable findings. After adjusting for mobile phone ownership, we observed that only those who engaged in mobile phone night-time activities more often, higher mobile phone calls on average per day and reported higher mobile phone addiction patterns were associated with worse headaches and sleep disturbances and lower HRQOL. We observed beneficial effects on neurocognitive development concerning the e-media exposure groups, across all three domains and more dominantly amongst moderate users, even after stratifying for age and socio-demographic factors.

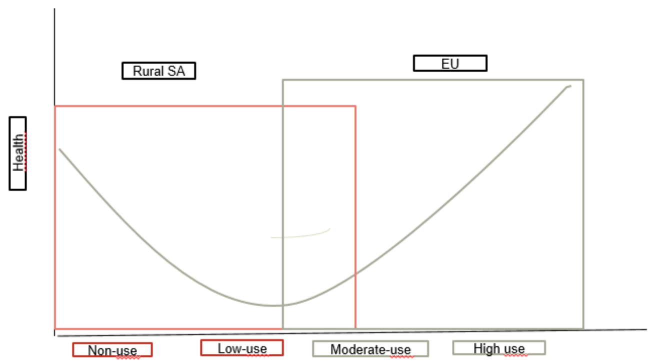


Figure 6 The u-shaped distribution between comparing rural LMIC e-media users to EU media use

The varying results in our health outcomes of moderate users may be indicative of the differences in e-media use patterns across the globe, illustrated in Figure 4. While our cohort of users represents a minority, and within this minority, e-media use on the high-scale in comparison to an EU setting is, in fact, moderate use, from which we observe lower effects on cognitive performance.

Furthermore, we learnt that it is crucial to include risk factors of health, specific to behaviour. We found that behavioural factors pertaining to problematic mobile phone use, mediated the effect between the exposure to e-media and these health outcomes. Thus, the behaviour of engaging in high exposure-related e-media use is problematic to health rather due to electronic-magnetic frequency emissions from the e-media device itself.

6.2.2 Implications and suggestions

We were limited by the low frequency of users in our exploration of an association between the content of e-media use and health effects. The low frequencies may be due to errors in self-reported data, presenting potential non-significant results observed, especially for total screen time. The small effect sizes may be underestimated due to statistical errors with the categorised method of analysis.

This analysis, therefore, warrants longitudinal follow-up data analysis toward causality, to correct for these errors, as well as account for residual confounding (for example personality characteristics or sporting activity) as a potential explanation; furthermore reduce random variability and inevitable chance findings, which may have occurred due to multiple testing in our models. However, in the latter regard, a sensitivity analysis was prioritised by using two cognitive test measures (speed and accuracy) per test to avoid systematic errors. In addition, standardised assessment through the CANTAB software tool lowered variation in test administration and potential systematic errors. Any major differences or difficulties that the administrator observed during a participant's testing was quantitatively recorded in the application and considered in the data distribution. Reverse causality may further be explored to account for an exposure group which may struggle to sleep and therefore use e-media more. We may not conclude the true estimate but rather the direction of association as highlighted across the repeated exposure analysis, coherent with our hypothesis and literature findings. Follow-up data will be analysed in the next CapSA steps to confirm the effect and rule out uncertainties, including potential errors due to small frequencies of high exposure groups, for example, posing large intervals in total screen time and limiting the true effect of this group.

Our cohort shows that in a generation where digitalization is at its peak, only 30% of e-media users exist in this rural LMIC context. The corresponding country statistics in 2013 reveals that only 10% of the country's households had access to the internet at home and thus the digital divide is a reality for this community. [60 121] The unfortunate disparities in the South African context between the rural and urban remain, and we see that even within each rural setting there are major differences between the rich and the poor, those who have and do not have, impacting HRQOL. The government has made attempts to correct this gap in service provision, rolling out free computer internet access in public areas across the country to support the disadvantaged, yet the rural areas continue to receive fewer resources, explaining South Africa as one of the top countries with the highest inequality rate. The percent of change between 2007-2017 shows minimum effort to reduce this Gini-Coefficient (from 0.65) and the lack of development to infrastructure, further impacts on the country's digital advancement, with continued daily power cuts, to distribute electricity countrywide. Furthermore, limited education and support are provided to the rural outskirts. Intervention projects have been implemented, like Melissa, under the SSARJ, for teachers to educate using e-learning in disadvantaged primary schools across the Western Cape, [122] and Siyakhula Living Lab focused on the Eastern Cape of South Africa to empower communities how to use the internet and troubleshoot. [59] Yet common problems are reported with the cost of communication, poor network, maintenance and limited resources for these rural schools. Since our findings reveal a benefit to cognitive development amongst moderate e-media users, the government should be advised to invest in these resources. On the other hand, problematic use of mobile phones and night-time awakenings warrants further awareness-raising in the community and schools, including the responsibility of parents of school children, to monitor and advocate for their child's education through preventing undisturbed sleep and reduced problematic mobile phone use. Since we can provide findings that this is a global problem, online applications may be used to support the awareness of these symptoms to users, while cell phone companies, may further be involved in the intervention of this problem, perhaps with built in night-time mode.

A recent study found an association between problematic cell phone use(PCPU) for text messaging and alcohol use; drunkenness at least once raised the odds of PCPU, while protective factors including longer hours of sleep, lowered the odds of PCPU amongst school-going children 11-13 years old. [46] These interactions should be further explored amongst those who report alcohol use in this cohort.

6.3 Maternal alcohol consumption and neurobehaviour

6.3.1 The association of lifestyle and behavioural factors on health and cognitive symptoms of children in rural South Africa

10% of mothers in the subgroup of guardian surveys reported gestational drinking, 27% reported past drinking, and 29% reported current drinking. Overall, we observed a non-significant negative trend across all three maternal alcohol exposure proxies and six neurocognitive health outcomes. The overall pattern of negative associations observed across the models in these preliminary steps of analysis is suggestive of adverse health effects from maternal alcohol exposure in this cohort. Non-significant estimates are potentially due to the small sample size which requires the power to identify the symptoms of chronic effects due to potential post-gestational exposure indicative of adverse home circumstances as concluded in current literature. [26] [123] BDD was not directly measured and this could further be a result of the non-significant findings. Household size was a predictor of lower spatial working memory and home language is a significant predictor of lower motor screening across all three exposure groups. Age, sex, and maternal employment were additional predictors of low executive functioning.

6.3.2 Implications suggestions

With only 482 guardian surveys available to date, the first author proposed binary exposure variables since there were low frequencies in the highest category of drinking. Collapsing the variables was thought to increase the power to determine the association, while a closer investigation using the method in this thesis to categorize the exposure proxies and identify small effects through a dose-response relationship will be further explored in future analysis with the full cohort. We see that capturing alcohol use behaviours are more complex in this cohort, due to the inconsistent response rate. Strategies to re-train fieldworkers with closer quality control will be implemented in the next data collection phase in the field during the next 512 guardian surveys. However, despite the attempts in the next steps, this is generally known to be a sensitive topic to capture accurately due to social desirability bias. Recall bias poses a further problem in this cohort of 9-16 year olds. Misclassification due to under-reporting and small sample sizes are more likely the reason for the limited evidence or potential errors of association between the effect of these environmental exposures and symptoms of executive functioning in children. The low response rate poses a problem to capture intensity measures of heavy-drinkers and the inability to get a true picture of whether the "Dop legacy" remains prevalent in these rural areas. [124] [125] In the current model, the suggestion would be to avoid measuring two exposures and reduce the socio-demographic factors to a combined measure. This factor is important to explore and adjust for in the longitudinal analysis if there may be confounding or potential interaction between the main exposure of pesticides and maternal alcohol exposure on neurobehaviour. [126]

6.4 Pesticide exposure and neurobehaviour

6.4.1 The association of physical environmental and behavioural factors on health and cognitive symptoms of children in rural South Africa

Approximately 50% of the cohort participated in social and work-related pesticide behaviours. We found that the headache symptom was consistently positively associated across all pesticide-related work and leisure exposure proxies, more dominantly for the younger age group. Eating and picking crops from the field, vineyard or orchard were the most detrimental activities to neurocognitive health outcomes, specific to areas of processing speed and attention in the older age group, while, in contrast, most detrimental to the memory performance of the younger age group. To adjust for potential errors in self-reported data with recall bias due to chronic exposure and lifestyle bias, the lifestyle factor of e-media and covariates were adjusted in the models on pesticide exposure to account for its confounding effect on the health outcomes under study, while the socio-demographic models with the sub-group indicated no confounding by SES. Despite the limitation of cross-sectional data and the need for our analysis to require repetitive measures with objective data, our observations are consistent with findings. Malathion was detected in CapSA air samples, and since new studies on mice reveal an association with chronic exposure from malathion on lowered spatial working memory, this preliminary observation in Chapter five should be further investigated.

Furthermore, we have restrictions in dimensions of these exposure variables which have no intensity and duration measure or environmental sampling patterns – for example, the presence of pesticides in water are seasonal and highest at spraying time which our survey variables do not account for in terms of when they engage in these behaviours. A study confirmed these seasonal variation patterns of pesticides on the surface level of water which were low during the dry season and high in frequency and concentrations during the rainy season and following gardening activities. [127] On the contrary, the CaPSA study found the presence of pesticides in surface level water in high concentrations during the drought season. [119] A more in-depth analysis is required on these pesticide exposure behaviours to determine the risk with the suggestion of an intensity score – children who engage in picking with and without PPE are more or less at risk and, additionally, children who pick socially or for work, face a higher increase in risk than others. A dose-effect relationship should be investigated with biomarker concentrations and exposure behaviours to establish high-risk groups. The CANTAB normative data, which became available toward the end of 2019, may account for more subtle neurobehavioral differences amongst the exposure groups in this cohort, as a 0.01 difference in neurocognitive functioning could be the difference between mild/moderate and severe intellectual disability. [6] Since self-reported proximity posed limitations in measuring differences in exposure, an exposure-matrix model is a next step of analysis in CapSA to gain more clarity on this environmental exposure gradient with the number of varying factors in these areas including distance from school and home to the nearby fields (illustrated in Figure 7), type of crop and type of chemical use. In addition, since DNA is proven to be an effective long-term biomarker for exposure, hair samples will be analysed, to identify additional individual variation in exposure and uptake. [128] [129]


Source Shala Mhlanga

Figures 7 The proximity of selected schools to the farming field (top) and the proximity of houses to the vineyards (bottom) in the study areas

6.4.2 Environmental findings from CapSA, confirming involuntary pesticide exposure

Data from farm surveys has been captured showing the variation of crop per area, indicating that peak spraying periods are from August to December and that there is much variation in the type of pesticide, concentration and compound used across three areas for different crops. The most commonly used are fungicides and insecticides, across the three areas, organophosphates, specifically chlorpyrifos is highly used in two areas, especially high in Grabouw. Of the 38 currently used pesticides measured in dust, air and soil across the three areas in villages and farms, 16 pesticides were above the limit of detection, with varying chemicals groups for insecticides and herbicides, the majority of OPs including the neurotoxic ingredients atrazine (Group2), diazinon (Group2), chlorpyrifos (Group3) and malathion (Group2), and two of which, carbaryl (Group2) and imidacloprid (Group3), are banned in the EU. [119] Interestingly, as indicated in the brackets, each is listed by Pesticide Action Network 2019 HHP's classification: group2 "long-term effects" and group3 "environmental toxicity". [20] Analysis of the small numbers of urine samples to date reveal the presence of pesticide metabolites in child participants reporting to live on the farm as well as in those reporting village residence and validated by a sub-study using wrist-band GPS monitoring on a small sample (n=99). [130] DDE and DDT were detected in both groups and known to be allowed for household pesticide use in SA, with only three quality studies available on chronic exposure to DDT in children, all three suggesting negative health impact of DDT on neurodevelopment. [131] The source of this DDT exposure is not yet clear; this could be due to household pesticide use, or it could be due to the problem of insufficient methods for disposing banned pesticides, and thus its persistent accumulation in the environment in South Africa. [132] [133] A systematic review of the chronic exposure to DDT as an indoor residential spray, legal in Africa, shows only nine out of 3,281 hits met the criteria for a quality study. Three out of those nine found evidence suggesting a negative impact of DDT on neurodevelopment. [134]

6.4.3 Implications and suggestions

The global situation of pesticide management reported by the FAO and WHO survey [135] revealed that one-third of the countries they investigated did not have guidelines for Highly Hazardous Pesticide (HHP) use, posing the problem of evaluating products if there are no guidelines. [136 135] The criteria and classification of the HHP initiative began in 2007 and was published in 2009, to which Glyphosate, was added in 2014 as a long term effect HHP. [137] Even still, CropLife international and five top member groups in the agrochemical market, have been exposed for profiting from 35% classified chronic and acute health and environmental HHP sales, the majority of which is Glyphosate (Figure 5), all predominantly sold to LMIC's. [20]

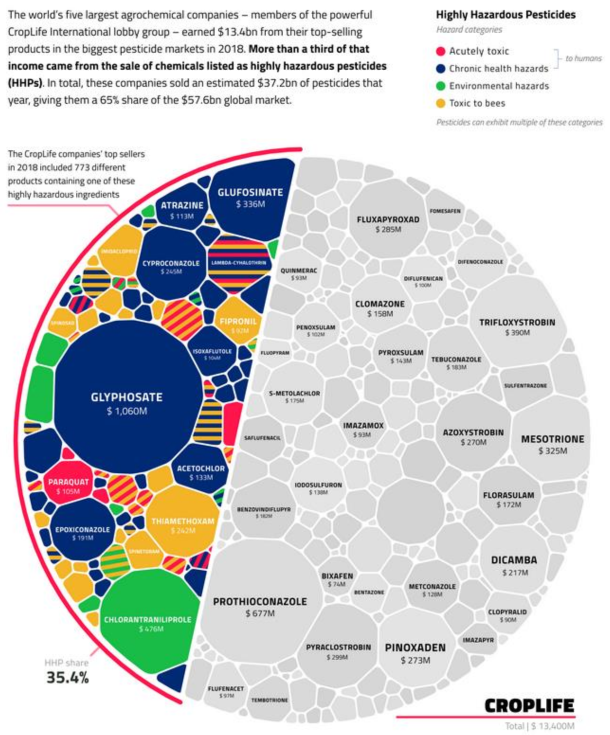


Figure 8 The pesticide sales of five top Croplife agrochemical companies include 35% of HHP's[20]

The existing conditions and current state of health and equity of the country shows a gap between government policy and practice in the rural areas of this LMIC. A parallel study in South Africa, using similar methods of assessment as CapSA, implemented an intervention relating to chronic exposure to mycotoxins on adverse health effects amongst subsistent maize farmers. They identified that authority regulations for safe pesticide use are not effective with regard to local farmers, and that integrated methods for interventions were ineffective due to problems with infrastructure and sustainable technology; furthermore, food security and the traditional use of mouldy maize were barriers to effective intervention. [138]

This factor of food security is often a compromise on health in the farming industry. Yet this too may be a result of unawareness or as a recent article on “sustainable intensification of cropping systems” [139] to use less insecticides, explains: “farmers need to have the right mindset to want to try- something has to push them in this direction of alternate methods of farming to yield the same harvest”. There are more emerging success stories in the South African context from which we can learn, including a new classification of 659 pesticides into a minimum list of acute and chronic risks to human health; [140] reduction of hazardous chemical use through techniques of farming with IPM (Integrated Pest Management); and alternate methods of farming, including Environmentally Friendly Alternate Pesticides (EcoSMART), conventional farming requiring less pesticide use and soil health methods, which have proven to yield the same harvest. [141] Climate change is another global health challenge affecting farming and crop security in the context of which these alternate methods of farming are proving to be successful regarding the security and sustainability of the industry and livelihood. [142]

These social and environmental determinants of health have further been confirmed in a recent study associating low nutrition in agribusiness children with low and non-farm income, low expenditure on food, and low educational status of caregivers. Nutritional education, diversification, and intensification of agribusiness were recommended. [143]

Non-profit organisations and lobby activist groups, Pesticide Action Network (PAN), launched a “World no pesticide use Day” to hold companies accountable for the violation of children’s rights in the UN Convention, including the right to life, to education, and highest standard of health, referencing the adverse effects of neurotoxic pesticides as the “silent pandemic” of learning disabilities and neurodevelopmental disorders.[144] [145] According to an investigation by PAN, “there is a huge disconnect between what those companies are saying in the international policy arena and what they are doing.” HIA does not include social determinants and is not prioritised in Sub-Saharan Africa and LMIC’s, yet it is a crucial aspect of corporate and government partnerships to protect human health from the industry. [146]

The African Charter on Welfare of Child Rights is an additional children’s rights policy attributable to the contextual vulnerabilities of children from apartheid. [147] In response, Malaysia lobbies for buffers between farms and schools. [148] France now also lobbies for buffer zones around households towards farmland in agricultural communities. [149] There are many online applications available to support the reporting of pesticide hazards in the field, safe use practice, labelling and protective measures in the step by step picture format, as well as technical and agronomic approaches for smallholder farmers. [150] However, given the barriers mentioned with e-media use in this context, children and families are disadvantaged due to the government’s lack of effective infrastructure and inequality.

The life cycle approach is expressed as the ideal method to investigate environmental exposure effects at different life stages, including epigenetic factors. The SDG three progress report in 2019, South Africa, highlights that although adolescent fertility has declined from 56 births per 1,000 to 44 in 2019, the level remains high in sub-Saharan Africa, 101 births per 1,000 adolescent woman. [151]

Another factor to consider is the mediator of genetics, specific to pesticides. It would be highly valuable to consider the variance in the presence of the chemical which may or may not metabolize the uptake of pesticides in children.

6.5 Covariates and neurobehaviour- potential predisposing and enabling risk factors

6.5.1 The association of social, economic and behavioural factors of neurocognitive and health symptoms outcomes

Headache severity was significantly positively associated with those reporting alcohol use and head injury (categorised into severe accident or potential Traumatic Brain Injury), across all our models in Chapters three and five. In connection with the top 10 causes for years lived with disability in 2017, headache disorder is listed second, and we see that the risk factors for Disability-Adjusted Life Years in South Africa include the predictors alcohol use and interpersonal violence.

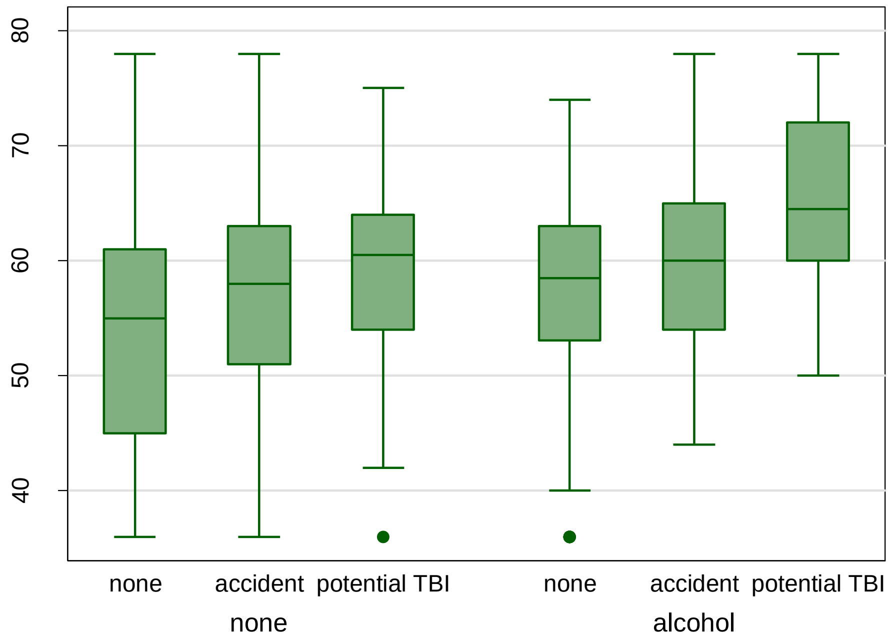


Figure 9 The associated pattern between those reporting alcohol use and head injury, in relation to the headache severity outcome score

Despite potential uncertainties and errors with self-reported health data such as recall bias or over-reporting by the group that experiences the health symptom, furthermore, those who are more educated about the health symptom may report more than those who are unsure. In addition, the main exposure to pesticides on the health outcomes may be modified by children who report alcohol and substance use, therefore, interaction variables are suggested in further analysis. We may understand these findings in relation to the current socio-economic status of this community and school context and discuss further.

6.5.2 The association of education and economic factors on health and safety practices

Education and poverty play a major role in the safe use and practices of pesticides on the farm, for both parents and children. This complex aspect has to be understood in the context of South Africa's political system in which the most disadvantaged communities in history were moved to the outskirts, lacking access to resources and isolated from quality services and standards of living. Household statistics for SA show that between 2006 and 2011, more than 10 million people in the country still lived in poverty, with the rich (20% of the population) possessing 61% of the country's wealth, and the poor only allotted 4.5% of the wealth. [60 121] Our study confirms this disparity, indicated by the high unemployment rate and 90% of households who are dependent on government grants.

Our sub-set analysis further reveals the significant predictor of pre-school and repeated grade on lower neurocognitive outcomes. 10% of children in the sub-set have not attended pre-school, a fact which is essential to include as a predictor in the ongoing analysis. These factors are essential components in our research findings to highlight government economic investment in early childhood development (ECD) education and the health of this community. ECD should be adjusted in the full set of guardian surveys in further research.

10% of the 482 guardian responses reported that their child received learner support. This intervention requires further investigation regarding its potential mediation effect between pesticide exposure and neurocognitive health outcome models. This could be a potential confounder, identifying a group of children who receive learner support due to identified cognitive difficulties in the classroom, yet the impact of this support will reveal its position in the model. The policy on screening, identification, assessment and support (SIAS) was released in 2014, to roll out the programmes aimed at addressing barriers to learning in schools and special needs schools, between 2017 and 2019 in the Western Cape. [152] Policy implementation began in 2015 with training teachers on how to identify children with difficulties and implement respective programmes, yet only one team of specialists, including one psychologist, was designated per district. The investment of resources to support education and learning in these disadvantaged groups is required. The SIAS programme initiated by the education department describes specific barriers and target programme areas to suggest health symptom education and to promote our findings on safe eating, safe play, and safe PPE use. Learners should be encouraged and made aware of how to identify the triggers (trauma, social, school or work-related stress, flu, etc.) of health symptoms which persist in their daily lives, to gain further insight into the reported symptoms and their causes as well as to provide prevention or intervention. [153]

Another crisis to consider in this context is the high drop-out rate in South African schools, with the statistics showing that approximately 60% of grade 1 children will drop-out rather than complete grade 12, and that only 52% of the age-appropriate learners remain enrolled in grade 12. [154] The study of South African predictors of drop out verses non-drop out populations in adolescents identified demographic predictors including alcohol, lack of individual motivation, number of days absent from school, and previously failed a grade. [154] This high-risk group has been identified across all models in our analysis and should be further studied in the next steps. Leisure experience is further predicted to increase drop out, with the lack of interest in school and engagement in healthy leisure (increasing peer-group affiliation, self-esteem and academic performance) leading to deviant behaviour. While results show that the individual alone does not contribute to the drop-out rate, the ecological perspective includes the predictors of poverty, family composition, social level and lack of interest in school, while teenage pregnancy and previous failure are also contributors. [154] Another study found that rural children's schooling was quite disrupted, with their model indicating grade 1 achievement, caregiver education, and cognitive test scores as significant predictors of school retention in South Africa. [155]

6.5.1.1 Home language and education

In the context of rural South Africa, the effects of low SES play a role in the health outcomes of this study; evidence has shown that, in LMIC, poverty is a risk factor for poorer cognitive performance and social and behavioural health and development. [156] Farm schools must also be understood in the context of their origin, so that our predictors of home language and lower neurocognitive values, as well as the differences in area and the impact of integrated learning on these different cultures, make sense, as an important finding that needs further investigation in case of confusion and of which the Ministry of Education and the government should be made aware. [157] We see that the implications of this legacy are perpetuated in the current context in the phenomenological phrase; "left behind in a democratic society: a case of some farm school primary schoolteachers of natural science in South Africa". [158] Furthermore, the more recent findings concerning the implications of integrating a global environment, including science and technology, in the South African economy – by assessing 11,000 grade 9 South African students in maths and science – indicate that they are hindered by strong associations as regards to not speaking the test language at home, financial constraints, and the condition of the school buildings. [159] Our significant predictor on household size in all three chapters of environmental exposure requires investigation in further analyses, with current studies on female employment and fertility showing that the odds of mothers finding work in the non-farm sector is lowered by 6%, and the effect of the number of children in non-farm work are problematic for older women and women with education, impacting on paid labour. [160] In turn, we see how this factor of low employment opportunities and paid labour for mothers in the farming communities influences the potential for child labour, especially amongst boys. [161]

Recent studies report that farmworkers (adults) in the South African context show non-compliance to the use of PPE as a result of the influence of workers' socio-cultural context (i.e. gender dynamics and social status), herbicide risk perceptions, and working conditions (i.e. environmental and logistical). [162] A study investigating the reasons for unsafe pesticide use by farmworkers uncovered miscommunication due to the language of instruction on the label of containers. Industry uses the incorrect terminology of “misuse” instead of “unintended use” for the end-user in the South African context, showing how influential these structures are regarding exposure and health effects. [163] This may prove even more detrimental if children are working with pesticide containers with limited understanding of the labels. Parents are a model for their safe use practices and yet there is another structure involved in this barrier to protective use. This refers to whether the industry considers children working in the field in their packaging and usage instructions. The awareness that children’s social engagement in picking and eating fruit may persist. France has used copper sulphate on vines to prevent children from eating crops from the vineyard. [128]

Yet we have to further investigate why school-going children in the 9-16 cohort are working. This uncertainty warrants further investigation on child labour practices in the community, given the prevalent gaps in African child labour law: “legislation favours industry, whereas we are dealing with countries which are basically agricultural; it covers the formal sector, where it is fairly unusual to find children at work; it does not apply to so-called ‘family’ businesses or domestic work or even agriculture, where child labour is most common. In other words, the law scarcely takes account of the real-life activities of children in Africa today at all.” [161] It is expressed that the main concern for children in this later age group, 14-15 years of age, is security of employment. [161] Recent literature confirms that children’s rights are evidently violated in the agricultural sector today as jobs in this sector offer neither decent incomes, work contracts nor sustainable livelihoods, and that agricultural workers are amongst those with the highest incidence of poverty in many countries. [136] Products and training should be adapted to the language and educational level of each community.

The existing Disease, Activity and School Children’s Health (DASH) project, investigating non communicable diseases in the Eastern Cape of South Africa, has effectively implemented a physical education programme to reduce the effect of non-communicable diseases on the health of children and their impact on schooling and in its second phase to roll-out to the Western Cape education department. This physical education programme is highly recommended for rolling out in these schools in order to support children with their health symptoms and to improve their focus on learning. [164] Additionally, health problems amongst teachers who are overburdened in a school system with one teacher to 40-50 children in a class, who themselves are overweight with evident health symptoms. A recent study highlights the challenges of teachers in farm schools, concluding that farm schools are still neglected with regards to resource allocation, and new educational policies should be implemented fairly. [158]

Statistical methods of factor analysis and structural equation modelling may be conducted to determine the complexity of influential factors on this health outcome, and identify the proximate to distal impacting factors to prioritize for effective strategic intervention in these rural areas.
The following section provides an overall perspective on the findings of this thesis, recommendations, the way forward, and conclusions.

7. Outlook

7.1 The dynamic systems at interplay when determining neurobehavioural risk factors among children in a rural LMIC context

In discussing the findings of this study, we note that each aspect is complex, involving varying elements and structures that need consideration, with both voluntary and involuntary exposures to environment and lifestyle determinants of health. It is vitally important to look at these findings in the context of the community and South Africa as a country before providing suggestions for an effective strategy.

SES is a major driving force on the state of health and advancement in this community. There are three dimensions of SES including employment, education and money, where the gradient of these three elements is correlated with health. The following Figure 6 illustrates the interplay of multiple structures and levels on the child’s environmental safety, education, future prospects and cognitive development.

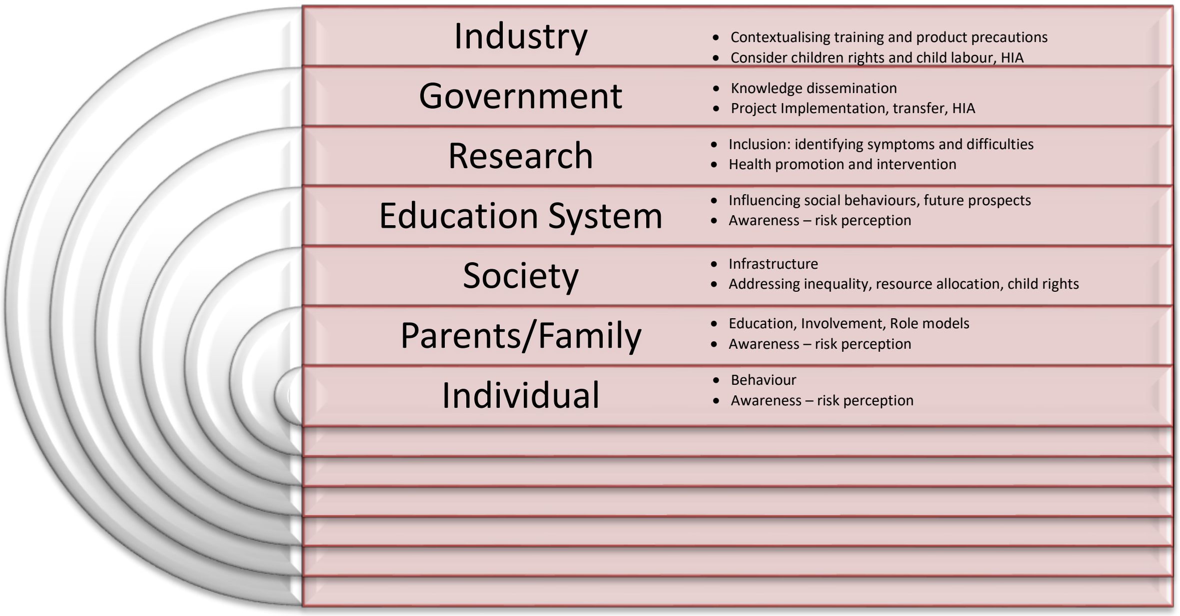


Figure 10 The varying structures related to a child's neurobehavioural health and development in rural SA

The following recommendations are provided to address reported health symptoms and preliminary findings of hazardous circumstances, despite our limited knowledge on the exact context of everyday settings, circumstances, experiences and perceptions or the direct causal pathway of environmental lifestyle factors.

7.1.1 Multi-layer framework

Since we observe multiple role players contributing toward the development of risk factors on the health outcomes in this community, including social structure, environmental and lifestyle influences, the need for the multi-layer framework, DPSEEA (driving forces, pressure, state, exposure, effect, action), used by the WHO to analyse different elements of causation, prevention and indicators in relation to environmental health hazards, may be beneficial to the best steps toward policy and action. [6] The hierarch of needs may be visualized to prioritise the direct and indirect risks and role players in this community, and identify the level of intervention/s [6]:

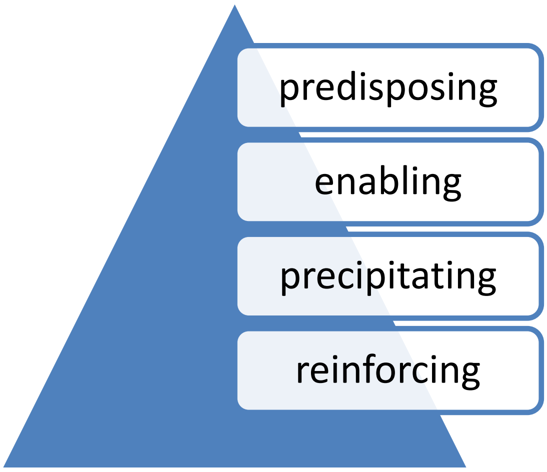


Figure 11 The hierarchy of factors in causation

The problem with this pyramid is determining which influence is greater. This hierarchy can be likened to Maslow's hierarchy of needs in social science, which may be applied to a rural LMIC whose distal influencing factors are inclusive of a human's most basic need at the bottom of the pyramid for food and housing, a sense of security and the ability to excel in education, employment and relationships. The higher you go, the higher you reach self-actualization. If your needs remain at the bottom, the need in every human to reach their full potential, emotionally, academically, and relationally through self-actualization, becomes less achievable.

Fundamental cause theory highlights that despite this knowledge, the debate about SES inequalities persist. Despite the efforts to potentially improve, for example, SES through employment opportunities only, to improve health, renders an outlook on yet another determinant of health – people value and invest in health differently across the globe. [156] An example of this is relevant to understanding our cohort – some people choose to use their good health to occupy a hazardous job to have high-employment. Another factor in this example is, therefore, why public health cannot be concerned with individual behaviour change only, very similar to why focusing on smokers only cannot be effective; industry plays a huge role in the inequality of health through advertising addictive behaviour and further providing these hazardous products for employees to work with in the agri-sector.

7.1.2 An integrated socio-ecological approach – recommendation in light of the discussion

Our results show that e-media use is beneficial for neurocognition and, potentially, for school retention in a poverty-stricken environment. Bridging the digital divide can enable countries and individuals to break the chains of poverty: "Affordable technologies in the hands of local communities can be effective engines of change, both social and material". [165] [60] E-media use cannot be restricted for all, instead, screening of problematic use behaviours are suggested for different structures including parents, existing school intervention programmes, and local health clinics.

7.2.1.1 E-media and farming for the future

An integrated approach may be composed of the activities identified, together with the problems and benefits outlined in this research study: Integrating e-media users and farmworkers in this cohort to empower them as life-long researchers, farmers for the future, and pioneers of farming methods, while educating their peers, family and community, may contribute to their livelihoods, advocating for safe practices, and improving the industry and economy of South Africa.

It would be to the interest of the government to invest in this group of youth, which represents the next generation, toward digitalization, farming, and the country's economy, and furthermore as a way to reach the goal of improving the countries GINI-coefficient by integrating the disparities in this rural community.

A collaborated effort between government departments of education and farming together with industry is suggested to develop an internship programme which may be integrated as a subject in the school curriculum. This may increase interest in school, technology learning, safe use practices, and implement training skills in the field to support the community of subsistence farmers, their future prospects of farming, the economy of South Africa and reduce the GINI-coefficient. This next generation of farmers will be empowered about environmental challenges such as climate change, improved farming methods, future education opportunities, and, at the same time, break the cycle of alcohol and drugs and social inequalities together with the inevitable improvement of health in these rural areas.

This long-term vision would require careful planning, proposals, partnerships, the interest and involvement of gatekeepers, and investment from the community and the structures at play for the provision of continuous HIA.

Thus, in recommending this opportunity to tackle multiple issues in this community at a multi-level approach, fundamental cause theory highlights that disentangling the multiple influences over the life cycle requires a model where the key interest of health practitioners are to identify whether interventions that change SES do in fact influence population health. [156] Identifying and evaluating effective strategies at local, national and international level is the goal in the next steps of the pesticide project which will be described below.

7.2 Effective pesticide intervention strategies

The pesticide intervention project was initiated by the Swiss principal investigator of SSAJR and funded by the SERI. Since SARChI has been renewed for the next five years, this project will be implemented in the SSAJR partnership in Global environmental health and CapSA. The goal is threefold: to network with stakeholders, experts in the agricultural field at grassroots level through existing farming projects and research, to integrate qualitative research in SSAJR pesticide project to determine existing effective farming strategies in the African farming hot-spots and, thirdly, to scale up exposure to HHP and health assessment in the CapSA study. The researcher/author will collaborate with this project after her PhD to conduct the qualitative research and project manage the objectives of this project.

Engaging stakeholders in this sector with other sources of scientific evidence, including systematic reviews, qualitative surveys, epidemiology exposure studies, will inform a global effective intervention strategy document, allowing interdisciplinary, international partnerships to initiate effective change at policy level, for the benefit of the farming community's wellbeing, the health of children and the safety of the environment as a whole.

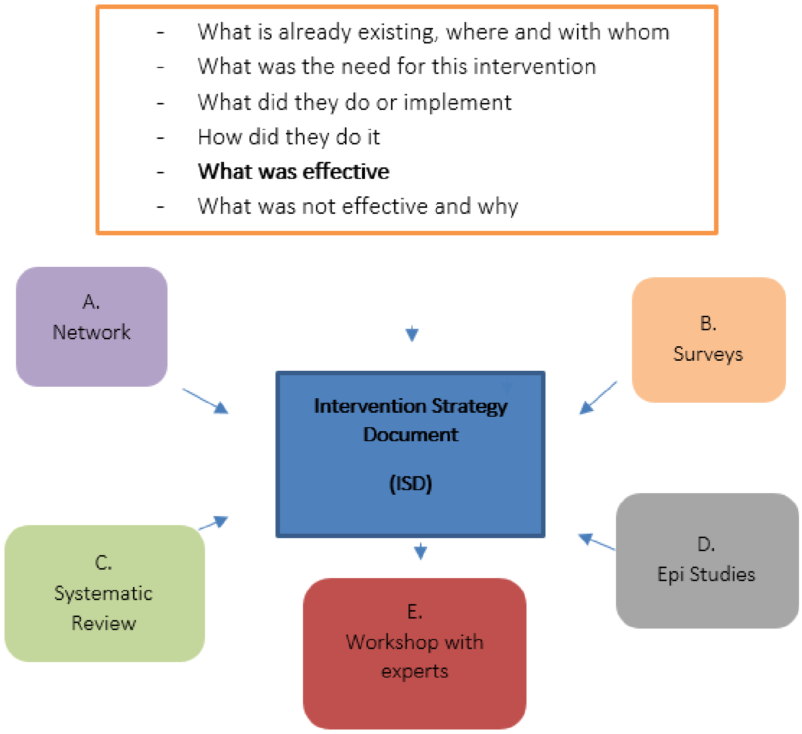


Figure 12 Project plan for the next steps on pesticide intervention

8. Conclusion

Cross-sectional analysis on the objectives of this thesis has provided initial insight into the exposure-related pesticide behaviours among children as well as the potential co-exposures from e-media use on the health symptoms and neurocognitive functioning in processing, memory and attention of children in this rural setting. High-risk exposure groups have been identified, implying a mediating effect between exposure and health outcome, specifically with regard to those eating crops from the vineyard or orchard and those picking crops and storing pesticide containers. While children woken up at night by their mobile phones and reporting problematic mobile phone use are at risk of headache severity, sleep disturbance and lower HRQOL than the non-exposure groups.

These are the first steps in understanding the complex, entangled risk factors in this rural LMIC country through a cohort study, to investigate chronic exposure effects. The use of epidemiological exposure assessment to include co-exposures to account for confounding, with a standardised software neurocognitive assessment tool, has supported our findings to identify hazardous environmental behaviours associated with symptoms and neurocognitive outcomes, characteristic of neurobehavioral disorders. We conclude that it is essential to include lifestyle behavioural influences in the steps toward understanding causal pathways between environment and neurobehaviour.

We see that the predisposing factors of the post-apartheid regime have an influence on the current state of unequal opportunities and limited resources in this environment, enabling a low SES in education and employment and ultimately poorer health and lifestyle behaviours. Furthermore, poor environmental quality with evidence of HHP present exceeding the regulatory limit is reinforced by industry sales and lack of guidelines and policy implementation for safe use, perpetuating the chronic physical environment exposure in this community. Another distal influential factor on these participants to high-risk exposure in pesticide work activities is possibly due to low SES and the inevitable food and employment insecurity, with more precipitating factors of low education on health and safety use. We could further potentially query whether the precipitating neurobehavioral difficulties in the classroom, reinforces these participants to work in the field.

We therefore understand that these uncertainties warrant longitudinal analysis with repeated measures and biomarkers to validate and account for further variation. In-depth analysis using qualitative interviews are recommended to understand the community's perceptions of health and environmental risks. Suggestions are to use existing support programmes within the school and community in creating awareness and integrating health promotion about the reported health symptoms of this cohort.

Government and Industry are to be involved in understanding the impact of low-quality environment on the health and future of this community. Awareness is crucial for the consequences on the country's economy to not invest in and develop the health and education of this generation Z toward digitalization and farming for the future, especially to equip and empower this generation by addressing public health challenges in a global climate crisis.

The plan ahead is to engage in establishing partnerships between stakeholders in the agricultural field and academia with a view to current practices and strategies for the protection of the health and safety of this community, and determine their effectiveness regarding implementation on a country-wide and global scale. Concomitantly, research on chronic exposure to pesticide use needs to be disseminated to government and industry structures so that they can assume responsibility and advance their involvement in the health and safety of the children and families in this community.

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10. Curriculum Vitae

Nationality: South African
DOB: 05.11.1984
Email: shalachetty7@gmail.com
Marital status: Married
Language: English (Proficient); Afrikaans; German (basic)

Background

I am a Social Scientist with a background in clinical and medical psychosocial and developmental practice from the early childhood to adolescence age groups and their families.

I completed a 3 year (theory, practical and qualitative research) Master's degree in Gestalt psychotherapy approach to assessment and intervention. Alongside my community-based practice, I started a clinical private practice and a pilot project to decentralize a tertiary level ECD intervention for primary health care.

This project led me to pursue academia training and research in global public health through a PhD in quantitative environmental exposure research, to assess broader risk factors on cognitive health, and acquire the skills to cognitively assess and quantify moderate mental and cognitive affects from chronic environmental exposures.
I continued in a one year post-doc position using a mixed methods design and transc-disciplinary approach to engage researchers and stakeholders on effective intervention strategies in Africa.

Education

PHD IN EPIDEMIOLOGY AND PUBLIC HEALTH - ENVIROMENTAL EXPOSURES AND HEALTH
UNIVERSITY OF BASEL (UNIBAS), SWITZERLAND *2020*

- Research topic: "an epidemiological cohort study of children and adolescents investigating neurobehavioral effects from pesticide exposure and electronic media use in South Africa"

GERMAN AS A FOREIGN LANGUAGE: LEVEL BI, 1/3 courses
UNIBAS, LANGUAGE CENTRE *2018*

MASTER OF SOCIAL WORK (ADVANCED GESTALT PLAY THERAPY)
NORTH WEST UNIVERISTY, CAPE TOWN, SOUTH AFRICA *2010- 2013*

- Specialised in Gestalt psychotherapy theory and practice (Children's Hospital) (individual and group work)
- Research topic on *the positive experiences of mothers of a child with Down Syndrome in the WC*

BACHELOR OF SOCIAL SCIENCE (HONOURS) IN CLINICAL PRACTICE IN SOCIAL WORK
UNIVERSITY OF CAPE TOWN, SOUTH AFRICA *2008*

- Awarded faculty scholarship for 2007
- Member of the Golden Key Society in 2008
- Research Thesis topic: The perceptions of educators on learner's difficulties in primary education

BACHELOR OF SOCIAL SCIENCES IN SOCIAL WORK (Specialising in Psychological Studies)
UNIVERSITY OF CAPE TOWN, SOUTH AFRICA *2005-2007*

- Awarded "Achievement for best skills in training"

MATRICULATION
ALEXANDER ROAD HIGH SCHOOL, PORT ELIZABETH *2002*

- Elected student leader (prefect)

Profession Skills

Clinical assessment, management, groupwork, therapeutic, research, networking, consulting, liaison across different disciplines and population groups, stakeholder engagement, training

Experience

POSTDOC SCIENTIFIC COLLABORATOR
SWISS TROPICAL & PUBLIC HEALTH INSTITUTE, UNIBAS *APRIL 2020 – MARCH 2021*
RESEARCH TOPIC: PESTICIDE INTERVENTIONS IN AFRICA AND STAKEHOLDER ENGAGEMENT

- Project Management – coordination of 4 parallel work packages
- Mixed-methods research with expert academics and stakeholders in the agricultural sector
- Research tasks -project design, survey (ODK), reviewing, data extraction, analysis (STATA, MaxQda), report writing
- Focus group discussion: planning, ethics, recruit, coordination and facilitation, report writing
- Member of Young Researchers Editorial Board (International Journal of Public Health) - reviewer, editor, handling-editor and anniversary editorial co-author (November 2018 to December 2020)
- IMPACT Conference, Swiss Implementation Science Network – Implementation Research Masterclasses
- BAG Task team (Sonja Merten) – review of literature on non-pharma interventions for COVID-19 (January 2021)

PHD CANDIDATE
SWISS TROPICAL & PUBLIC HEALTH INSTITUTE, UNIBAS *SEPTEMBER 2016-MARCH 2020*
RESEARCH PROJECT: SA-SWISS RESEARCH CHAIR IN GLOBAL ENVIRO HEALTH (SARCHI)
RESEARCH TITLE: "*an epidemiological cohort study of children and adolescents investigating neurobehavioral effects from pesticide exposure and electronic media use in South Africa*"

- Project Management – fieldworker hiring and training, implementation, project coordination, data quality control
- Research: design, CANTAB neurocognitive assessments, surveys – quality of life, headache &addiction tools, ethics data monitoring, cleaning and analysis (linear and logistic regression models using STATA) graphs using R, ArcGIS
- Public Health and Epidemiology Coursework (39 ECTS)
- Publications:

  Chetty-Mhlanga S, Basera W, Fuhrimann S, Probst-Hensch N, Delport S, Mugari M, et al. A prospective cohort study of school-going children investigating reproductive and neurobehavioral health effects due to environmental pesticide exposure in the Western Cape, South Africa: study protocol. BMC Public Health 2018; 18:857. doi:10.1186/s12889-018-5783-0

  Chetty-Mhlanga S, Basera W, Aqiel Dalvie M, *et al*. A study of school-going children on the neurobehavior and currently used agricultural pesticide exposure in the rural western cape, South Africa. Occup Environ Med, BMJ. 2018; 75(Suppl1):A11.2. doi: 10.1136/oemed-2018-ISEEabstracts.27

  Foerster M, Henneke A, Chetty-Mhlanga S, Röösli M. Impact of Adolescents' Screen Time and Nocturnal Mobile Phone-Related Awakenings on Sleep and General Health Symptoms: Cohort Study. Int J Environ Res Public Health 2019; 16:518. doi:10.3390/ijerph16030518

  Shala Chetty-Mhlanga, Samuel Fuhriman, Marloes Eftens, Wisdom Basera, Stella Hartinger, Mohammed Aqiel Dalvie, Martin Röösli. Electronic media use, its problematic aspects on the health symptoms and neurocognitive functioning of children in the rural Western Cape region of South Africa. Environ Res. doi.org/10.1016/j.envres.2020.109315

  Chetty-Mhlanga, S., Fuhriman, S., Eftens, M., Basera, W., Röösli, M., Dalvie, AM. Association of activities related to pesticide exposure on headache severity and neurodevelopment of school-children in the rural agricultural farmlands of the Western Cape of South Africa. Environ Int 2020 Nov 7;146:106237.doi: 10.1016/j.envint.2020.106237

  Vasileios Nittas, Diana Buitrago-Garcia, Shala Chetty-Mhlanga, Pauline Yongeun Grimm , Germán Guerra, Chandni Patel, Peter Francis Raguindin. Future public health governance: investing in young professionals. Int J Public Health 2020 Nov 3;1-2. doi: 10.1007/s00038-020-01521-0.

  Regina N Molomo, Wisdom Basera, Shala Chetty-Mhlanga, Samuel Fuhrimann, Martin Röösli, Aqiel Dalvie. Relation between organophosphate pesticide metabolite concentrations with pesticide exposures, SOCIO-ECONOMIC factors. and lifestyles: A cross-sectional study among school BOYS IN the rural western cape, South Africa Environment Pollution Journal, 15 April 2021, doi.org/10.1016/j.envpol.2021.116660.

  Shala Chetty-Mhlanga, Paola Viglietti, Martin Röösli, Aqiel Dalvie. Maternal alcohol use and smoking on neurocognitive function of school children in the rural Western Cape. (Submitted to Neurotoxicology)

- Conference presentations:
  Oral presentation: International Society for Environmental Epidemiology (ISEE Young), 2018
  Poster Presentation:
  Shala Chetty-Mhlanga, Mohammed Aqiel Dalvie, Martin Röösli (on behalf of the CaPSA team) "Electronic media, problematic aspects and neurobehavioral functioning of children in the rural Western Cape of South Africa," Swiss Public Health Conference- *Child and Adolescent Public Health*, Winterthur (2019)

- Lecture, Seminar and Workshop presentations:
  -Lecture presentation at Swiss TPH weekly MSc and PhD Seminar-
  "Advances in Infection Biology, Epidemiology and Global Public Health" October, 2019 (41 student attendees)
  -Seminar presentation, School of Public Health and Family Medicine, University of Cape Town, SA, March 2019
  -Annual workshop presentations at SA-Swiss Bilateral research in global environment health, April 2017-2020

- Supervision (Co-supervisor):
  UCT, MPH student- Maternal alcohol exposure on the neurocognition of children in the WC, graduated in 2020

INTERNSHIP DURING PHD (20%) (BASEL)

INTERNATIONAL JOURNAL OF PUBLIC HEALTH (IJHPH SPRINGER PUBLICATION) *AUGUST 2019-OCTOBER 2019*

- Assistant to managing editor
- Research project proposal- Influential factors on the citations of IJPH publications

RESEARCH FIELDWORKER/AIR POLLUTION MONITOR (CAPE TOWN)

COLLABORATION WITH SARCHI – CPUT, UCT AND Swiss TPH *OCTOBER 2015-AUGUST 2016*

- Trained on sampling, technology and handling of equipment
- Setting up sampling stations in 4 neighborhoods in the Western Cape
- Data management and quality control

GROUP FACILITATOR - Becoming Professional (BP) and Becoming a Health Professional (BHP) Courses

UCT (FACULTY OF HEALTH SCIENCES- DEPT OF PUBLIC HEALTH AND FAMILY MEDICINE) *FEBRUARY 2015 - AUGUST 2016*

- Teaching curriculum by facilitating experiential groups with Health Science students (n=12&24)
- Individual and group preparation with all facilitators by Course Conveners via experiential group training
- Mentoring students one-on-one throughout the course
- Assessing and grading written and practical course outcomes

MEDICAL SOCIAL WORKER

TYGERBERG HOSPITAL - CAREL DU TOIT CENTRE (CAPE TOWN) *FEBRUARY 2014 – SEPTEMER 2015*

- Gestalt Psychotherapy with children and adolescents
- Case management of children with neurodevelopmental diagnoses within multi-disciplinary teams
- Evaluating and counseling families referred from private or public health facilities
- Assessing family needs and developing support programs
- Facilitating parent support groups and small business training workshops
- Training and supervising staff on professional development workshops
- Strategic planning and development of a decentralized community project for accessible primary health care intervention with health professionals

CLINICAL SOCIAL WORKER (**CAPE TOWN)**

PRIVATE PRACTICE (registered with SACSSP; Medical ICD codes) *APRIL 2012 – OCTOBER 2015*

- Individual Gestalt Psychotherapy (primary and high school learners)
- Family Counselling with parents of learners
- Facilitating therapeutic group with Special Needs Learners on Life-skills Interventions (Inclusive Unit)

COMMUNITY LIAISON OFFICER (**CAPE TOWN)** *April 2012 - Dec 2013*

PSYCHIATRIC STIKLAND HOSPITAL - THE WESTERN CAPE FORUM FOR INTELLECTUAL DISABILITY [ID]

- Facilitating therapeutic support groups (empowering goals, addressing self-esteem, relationships & communication) with young adults diagnosed with physical, intellectual and mental disabilities
- Training Health Care Workers on life-skills, sexuality, HIV/AIDS, the work place, development and ID
- Liaison and needs assessments of service providers (150 member organizations) in the field of ID
- Developing yearly training program and coordinating training for members
- Capturing statistics of training and report writing
- Community awareness on ID in rural and urban areas of the Western Cape
- Case management with families and health professionals

FAMILY COUNSELLOR (CAPE TOWN) *January 2009 - March 2012*

RED CROSS CHILDREN'S HOSPITAL- AUTISM WESTERN CAPE; ECD CENTRE

- Individual and group Gestalt Psychotherapy for neuro-typical children presenting with psychosomatic symptoms
- Individual bereavement and supportive counseling for parents of children diagnosed with a disability
- Facilitation of therapeutic parent support groups
- Facilitating self-advocacy groups with young adults who have disabilities
- Individual Early Childhood Global developmental assessments with children (0-7yrs) diagnosed with a disability
- Developing and advising home intervention programs and resources for children, families and community
- Case management with families and health professionals

AUPAIR (U.S.A and U.K) *JAN 2003-DEC 2004*

- Living with family and caring for school children between 2-8years old
- Attending program and network requirements including monthly workshops, CPR training and college courses