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Maternal alcohol consumption and socio-demographic determinants of neurocognitive function of school children in the rural Western Cape

A dissertation submitted in partial fulfilment of the requirements for the degree

MASTER OF PUBLIC HEALTH

(Epidemiology and Biostatistics)

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Date: 4 February 2020

Plagiarism Declaration

I, Paola Viglietti, student number, VGLPAO001 declare that the work I have submitted is my own and where the work of others has been used (whether quoted verbatim, paraphrased or referred to) it has been attributed and acknowledged.

Date: 4 February 2020

Signature: Signed by candidate

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Abstract

Background. Within the South African context there is a large body of research regarding the associations between maternal gestational drinking and diagnosable child FASDs. However, there remains a paucity of local research regarding the impacts of other kinds of maternal drinking behaviours (e.g. past and present maternal drinking) and related socio-demographic factors on developmentally sensitive areas of child neurocognitive functioning, such as executive functioning (EF).

Methods. This study was cross-sectional in design, utilising a gender balanced sample of N=464 children between the ages of 9.00 and 15.12 (year.months) in three rural areas within the Western Cape. Information regarding maternal drinking behaviours (before, during and after pregnancy) and related socio-demographic factors was collected via structured interviews with mothers or proxy respondents. Six subtests from the Cambridge Automated Neuropsychological Battery (CANTAB), were used to assess three aspects of child EF namely: (1) *processing speed*, assessed by the MOT and RTI subtests, (2) *attention*, assessed by the MTT and RVP subtests and (3) *memory*, assessed by the SWM and PAL subtests.

Findings. For all three maternal alcohol use behaviours examined, there was an apparent non-significant trend whereby children of mothers who reported alcohol use (before, during and after pregnancy) performed worse (on average) than children of mothers reporting non-alcohol use on the EF subtests. Several of the socio-demographic factors were found to act as significant predictors of subtest specific EF performance including child sex (RTI: B=.46, p<.01; MTT: B=.05, p<.05), child age (RTI: B=.27, p<.05; MTT: B=.11, p<.01), home language (MOT: B=-.13, p<.05), maternal employment (MTT: B=-.04, p<.05) and household size (SWM: B=-1.29, p<.05).

Conclusions. These study findings provide initial insights into the impacts of different types of maternal drinking behaviours and related socio-demographic factors on child EF outcomes within the context of an LMIC, South Africa.

Key words: maternal alcohol consumption behaviours, maternal drinking behaviours, maternal alcohol use, socio-demographic factors, child neurocognitive functioning, child executive functioning (EF), Cambridge Automated Neuropsychological Battery (CANTAB), lower-middle income countries (LMICs), developing countries.

Dissertation Overview

As per the requirements for MPH dissertations within the department of Public Health and Family Medicine at the University of Cape Town (UCT), the current dissertation is constituted of three separate components that each have their own pagination, index pages and appendices.

Part I: Project Proposal

Part II: Literature Review

Part III: Manuscript

List of abbreviations

ARBD – Alcohol related birth defects

ARND - Alcohol related neurodevelopmental disorder

CANTAB – Cambridge Neuropsychological Test Automated Battery

CEOHR - Centre for Environmental and Occupational Health Research

CNS – Central nervous system

BDDs – Neurobehavioural and neurodevelopmental disorders

ECD – Early childhood development

EF – Executive functioning

EFs – Executive functions

FAE – Fetal alcohol effects

FAS – Fetal alcohol spectrum

FASDs – Fetal alcohol spectrum disorders

GCS – Glasgow coma scale

GMDS – Griffiths Mental Development Scales

HD – Hazardous drinking

HREC – Human Research Ethics Committee

IPV – Inter-personal violence

LMICs – Lower-middle income countries

KZN – Kwa-Zulu Natal

MR – Multiple regression

NC – Northern Cape

ODK – Open data kit

PDD – Pervasive developmental disorder

PFAS – Partial fetal alcohol syndrome

RCPMS – Raven's Coloured Progressive Matrices

SES – Socio-economic status

TBI – Traumatic brain injury

WC – Western Cape

SECTION I: Project Proposal

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1. Introduction

Several studies conducted within the Western Cape (WC), South Africa have repeatedly found exceptionally high levels of Fetal Alcohol Syndrome (FAS) and Fetal Alcohol Spectrum Disorders (FASDs) amongst children in this area (1-5). To put this into perspective, the rates of FAS in first graders in the Western Cape are 18-141 times greater than rates of FAS in the United States (1). As such maternal gestational alcohol consumption continues to pose a major public health problem with regards to early childhood development (ECD) within the Western Cape, and specifically within rural farm areas as a legacy of the 'dop system'(6-9). It is notable that while local research has focused on maternal gestational drinking as a biological determinant of poor child neurocognitive outcomes, such as FAS and other FASDs (1-5), within the international research literature past (antenatal) and present (postnatal) maternal drinking behaviours and related socio-demographic factors are increasingly being recognized as important social determinants of child neurocognitive outcomes (10-23).

Specifically, several studies have shown that past and present maternal alcohol consumption behaviors along with related socio-demographic factors can have profound impacts on child neurocognitive functioning, especially in developmentally sensitive areas such as intellectual, behavioural and executive functioning (10-15). However, as the research conducted within the South African context continues to focus on the prevalence of 'full blown' FASDs, and on FAS in particular, there remains limited research regarding the impacts of both biological and socio-demographic factors on developmentally sensitive areas of child neurocognitive functioning, such as child executive functioning (24, 25). As such, this study aims to examine the impacts of both biological and socio-demographic factors on child neurocognitive functioning, with a specific focus on how these determinants predict children's performance on tasks of executive functioning (EF).

1.1 Problem identification

Whilst there is a large body of local and international research pertaining to maternal alcohol consumption during pregnancy as a biological determinant of negative child neurocognitive outcomes in the form of FASDs (1-5, 26-29), there is limited local research regarding how past and current maternal alcohol use behaviours come together with related socio-demographic factors to influence developmentally sensitive child neurocognitive outcomes (24, 25). From a biological standpoint, research has been able to show that maternal alcohol consumption during pregnancy has particularly detrimental effects on the in-utero development of the central nervous system (CNS), negatively impacting on children's neurocognitive functioning during childhood (26-29). However, recent international research suggests that children's neurocognitive functioning is not only affected by direct contact with teratogens, such as alcohol during pregnancy, but is also affected by past and current maternal alcohol use and related socio-demographic factors which exist within children's environments (10-22).

One recent research study conducted within the Western Cape, has provided initial evidence to suggest that past and current maternal alcohol consumption behaviours are significantly associated with child neurobehavioural and neurodevelopmental disorders (BDDs) (24). Another recent research study conducted in Kwazulu-Natal (KZN) found that maternal hazardous drinking (HD) was significantly associated with poorer child executive functioning outcomes (25). These studies provide initial evidence to suggest that other forms of maternal alcohol consumption behaviours (apart from maternal gestational drinking) also have the potential to negatively impact on developmentally sensitive child neurocognitive outcomes, a finding which requires corroboration through further local research.

Furthermore, there is a growing body of international research which suggests that socio-demographic factors which exist in children's environment including: household size, home language, parental marital status, parental employment, maternal education, child age, and child sex, also have profound effects on child neurocognitive functioning (16-21). However there remains limited research regarding the impacts of these socio-demographic factors on sensitive neurocognitive outcomes, such as child executive functioning, within the context of developing countries (30-33). As such, there is a need for further research regarding the impacts of these socio-demographic factors on developmentally sensitive child neurocognitive outcomes such as child executive functioning, within the context of developing countries like South Africa.

1.2 Rationale and motivation

Within the context of the Western Cape, South Africa, due to the high prevalence of FAS and FASDs there is a continued need for public health interventions to target the prevention of maternal gestational drinking (1-5). However, in light of a growing body of international research there is growing evidence to suggest that socio-demographic factors in children's environments also have profound impacts on child health outcomes and on developmentally sensitive areas of child neurocognitive functioning, such as executive functioning in particular (10-15). As such there appears to be a growing need for public health interventions, and specifically ECD interventions, to recognize and address not only the biological determinants but the socio-demographic determinants of child executive functioning (30, 31). In essence, there appears to be a pressing need to acknowledge the contextual drivers of child executive functioning outcomes within the context of South Africa, so that there is an increased understanding of how poor executive functioning outcomes can be prevented in this context.

2. Literature Review

2.2 Contextual background: The determinants of child health outcomes in South Africa

Although South Africa was democratized in 1994 the legacy of apartheid has meant that the living and working conditions on many South African farms remains poor (7-9). Specifically, within the rural farm areas of the Western Cape, the additional legacy of the 'dop system,' has further impoverished farm workers in this area (7, 8). The dop system, initially introduced by Dutch settlers to the Cape, refers to the practice of paying part of farm workers' wages in unrefined wine, a practice which has continued despite its illegality (7-9). This system has been used to exert control over farm workers, keeping them and their families in an impoverished position over generations through the creation of a culture of alcohol intake and dependence (7-9).

It is notable that although the dop system has had a detrimental impact on the health and well-being of the farm working community in the Western Cape as a whole, this system and the social conditions it has engendered over time continue to have particularly detrimental effects on mothers and their children in this community (7-9). Women constitute around 30% of the workforce on commercial farms and are more than twice as likely than men to be hired as casual labourers with low job security (8, 9). Moreover, the low minimum wage in South Africa means that around two thirds of farm-working households live in waged poverty (8, 9). Living in poverty and having low job security impact upon maternal mental health, with research showing that mothers in this region often use alcohol as a coping mechanism to deal with feelings of low self-esteem and depression (7-9). Thus, social stressors that mothers experience have implications for maternal alcohol consumption behaviours before, during and after pregnancy which each pose a risk to child neurocognitive development and executive functioning capabilities (24, 25).

2.3 Fetal alcohol spectrum disorders: Diagnostic issues & problems surrounding self-report

A diagnosis of FAS requires that, along with evidence of maternal gestational drinking, specific symptoms are present in the child including: craniofacial dysmorphology, growth restriction and CNS dysfunction (34-40). However, it is often the case that not all of these symptoms are present in children exposed to alcohol in utero (41). In the past, diagnostic terms including partial FAS (PFAS), fetal alcohol effects (FAE), alcohol related neurodevelopmental disorder (ARND) and alcohol related birth defects (ARBD) have been used to describe individuals who did not display all the required symptoms for FAS (36, 39). However, within the more recent literature 'FASD' has been introduced as an umbrella term to encompass all diagnoses and clinical presentations displayed by children exposed to alcohol in utero, acknowledging the spectrum of effects that prenatal alcohol exposure can result in (36, 39). Although the disorders that fall under the umbrella of FASD are diagnostically distinct it is notable that they share a key feature: neurocognitive dysfunction, and problems with executive functioning in particular (35-40).

As mentioned above, in order to diagnose any disorder that falls within the FASD spectrum (such as FAS, PFAS, FAE, ARND, ARBD) there needs to be evidence of maternal gestational drinking (41, 42). However, previous research has repeatedly highlighted how difficult it is to diagnose and distinguish between the disorders falling within the FASD spectrum, as firstly it is difficult ascertain whether a child was indeed exposed to alcohol in utero, to what extent they were exposed and for how long (41-44). Problems with determining exposure stem from the fact that there is no reliable biological method to detect low to moderate levels of maternal alcohol consumption during pregnancy, which is problematic as research has shown that even low levels of exposure to alcohol in utero can lead to negative child health outcomes (45, 46). Not having a reliable and objective bio-marker of maternal alcohol use during pregnancy means that researchers are forced to rely largely on self-report measures of maternal gestational drinking, which are considered unreliable due to response bias (44, 46).

However, more recent research comparing concurrent and retrospective reports of maternal drinking has suggested that the use of concurrent self-report measures of maternal drinking results in the under-reporting of maternal gestational drinking (44), whilst retrospective reports of maternal drinking during pregnancy have been shown to act as better predictors of child health outcomes (46). In light of these research findings, it appears that the use of retrospective self-report may be a more reliable measure of maternal gestational drinking than previously thought.

2.4 A change in focus: The biological and socio-demographic determinants of child neurocognitive outcomes

Within the research literature there is a concerted focus on the neurocognitive profiles of children who were exposed to alcohol in utero (34-40). Specifically, there is a substantial body of research which has endeavored to specify the neurocognitive and neurobehavioral profiles of children diagnosed with fetal alcohol syndrome (FAS) and fetal alcohol spectrum disorders (FASDs) (34-40). The research concerning the neurocognitive profiles of children with FASDs provides us with important insights into how alcohol use during pregnancy affects child neurocognitive development and executive functioning (34-40). Specifically, this research has repeatedly shown that problems with executive functioning (EF), as displayed by poor performance on EF tasks, is a cardinal feature of children exposed to alcohol in utero (34-40).

However, although there is a growing body of research regarding the neurocognitive profiles of children exposed to alcohol in utero (i.e. those who exist on the FASD spectrum), few research studies have also taken into consideration the effects of specific socio-demographic factors in children's environments, which have also been shown to impact child neurocognitive functioning (16-21). As such, within the context of a developing country, where children are known to be more likely to encounter adverse socio-demographic factors, there is a need for further research to examine the impacts of these socio-demographic factors along with the impacts of known biological factors (such as maternal gestational alcohol use) on child neurocognitive outcomes and particularly on developmentally sensitive areas, such as executive functioning (30-33).

2.5 Executive Functioning: The construct, its biological substrates and development

Within the research literature, it has been repeatedly emphasized that a specific area of neurocognitive functioning know as executive functioning (EF) is especially sensitive to disruption both from biological (28, 29) and socio-demographic factors (16-21). However, we have yet to discuss what the construct of EF refers to and what biological substrates are understood to underlie this construct (47, 48).

As EF is a multifaceted construct, understood to be sub-served of several different functions, this aspect of neurocognitive functioning is difficult to define (47, 48). In the literature, EF is described to encompass higher order cognitive processes that drive the conscious control of thought and action, generally to realize a goal (47-49). The functional capacities contained within the broader EF umbrella are understood to include: planning, inhibition, working memory, organized search, set shifting, strategy employment, flexible problem solving, attentional allocation as well as self-monitoring and assessment (47-49). From historical neuropsychological cases the frontal cortex of the brain has been determined to be the seat of human EF capabilities, as damage or dysfunction within this area has been shown to lead to poor performance on EF tasks (47-49).

It is important to note that unlike many other areas of neurocognitive functioning, executive functions (EFs) follow a protracted developmental course through childhood into adolescence, only reaching full maturation during adulthood (48). As such, because EFs follow a long developmental course they are particularly vulnerable to both harmful biological exposures prenatally and socio-demographic exposures in children's antenatal and postnatal environments (48, 49). Notably, research has shown that exposure to alcohol in utero effects the development of the frontal cortex, suggesting a potential explanation for EF deficits being a cardinal feature of FASDs (28, 29).

However, there is also a growing body of research which suggests that adverse socio-demographic exposures also have a profound effect on the structure and function of the frontal lobes in children, resulting in EF deficits (20-22, 50, 51). Examining these two bodies of research together it is apparent that there is a need for further local research to provide a more in-depth understanding of how both biological and socio-demographic factors come together to influence child neurocognitive functioning, and particularly how these factors combine to impact on child executive functioning.

3. Research aim & objectives

3.1 Aim

The aim of the current study is to determine the relative impacts of both biological and socio-demographic factors on neurocognitive functioning of children living in rural agricultural areas within the Western Cape, South Africa. More specifically, this study aims to determine how much variation in performance on EF tasks can be accounted for by certain biological and socio-demographic predictors presented within the research literature.

3.2 Objectives

1. To briefly describe the socio-demographic characteristics of the child population (ages 9-15 years) and the mothers of said child population.
2. To determine the percentage of children's mothers reporting antenatal (past), prenatal (during pregnancy) and current (postnatal) alcohol consumption behaviours.
3. To investigate the impacts of maternal alcohol consumption behaviours (before during and after pregnancy) and related socio-demographic factors (namely: household size, home language, parental marital status, maternal education, maternal employment, child age and child sex) on child EF abilities.

4. Methods

4.1 Study design

The current study is a sub-study of an ongoing research entitled "*A prospective cohort study of school-going children investigating reproductive and neurobehavioral effects due to environmental pesticide exposure in the Western Cape, South Africa*" being undertaken by a bilateral research team working within the UCT's Centre for Environmental and Occupational Health Research (CEOHR) and Swiss Tropical and Public Health Institute (TPH) (52). This study has ethical approval from the Human Research Ethics Committee (HREC) of UCT's Health Science faculty, with the HREC reference number being 234/2009 (Appendix 8). This ongoing research project is a longitudinal study of school children from the rural Western Cape that consists of a baseline study which has already begun in April 2017 and a follow-up that will be conducted in May 2019 (52).

During the baseline study, data has been collected from the children at the participating schools and data has begun to be collected from parents and guardians at their place of residence using a structured interview. The cohort of children were recruited from six different schools within three agriculturally intensive areas in the Western Cape (52). Falling under this ongoing longitudinal research project, the current study will be cross-sectional in design. The current study will use child cognitive data already collected through ongoing pesticide research project and will directly collect parent and guardian data through the use of a structured parent/guardian questionnaire to address the current study's main aim which is to investigate the determinants of child executive functioning (EF) within rural agricultural areas of the Western Cape.

4.2 Sampling

The overarching pesticide research project, from which the current study will be using a portion of secondary data, used a purposive sampling strategy to recruit N=1001 child participants between the ages of 9 to 16 years from schools within three agricultural areas where pesticide spraying is known to take place (52). Schools in the Hex River Valley, Grabouw, and Piketberg were recruited as previous research studies have detected the presence of pesticides among farm workers and within water supplies as well as other environmental mediums in these areas (52-54). Children in the overarching study were enrolled in equal numbers with regards to age, gender, agricultural area and whether they attended a farm or town school (52). Initially, before the recruitment and enrolment process began, permission from the Department of Education (DOE) was sought (Appendix 1). After permission was given by the DOE, schools in the three agricultural areas were approached with a permission letter inviting the school board and principal to consent to participate in the study (Appendix 2).

It is notable that in all three study areas there were a total of 32 schools, however only combined primary and intermediate schools were approached to participate (to prevent loss to follow up due to matriculation) (52). Altogether, 22 intermediate schools were approached of which 12 agreed to participate and 7 combined schools were approached of which 4 agreed to participate (52). Once a school gave their permission to participate, parents were sent permission letters through the school administrative system which asked if the parent and their child would be willing and able to participate in the study (Appendix 3). Parents who returned permission letters were contacted to set up a time for a researcher to go to their home to complete the informed consent process.

4.3.1 Exclusion criteria

There are three exclusion criteria for the current study: (1) evidence of severe traumatic brain injury as determined by a set of questions based on the Glasgow Coma Scale (GCS), (2) diagnosed health outcome or Pervasive Developmental Disorder (PDD) known to impact on child neurocognitive functioning and (3) use of prescribed medication that could influence child neurocognitive performance (such as Ritalin or Concerta).

4.4 Sample size

Sample size estimates presented here have been calculated based on two FAS prevalence studies done in the Western Cape region (1, 2). The study by May and colleagues (1) found the prevalence of FAS to be 40.5-46.5 per 1000 children and the study by Vijoen and colleagues (2) found the prevalence of FAS to be 65.2-74.2 per 1000 children, taking an average of these two studies gives and estimated prevalence of FAS to be 56.6 per 1000 children (or a prevalence of 5.66%). Although these studies examined FAS prevalence and did not focus on child neurocognitive outcomes such as EF, one of the main characteristics that typifies FAS are problems with child EF (34-40).

As such these FAS prevalence studies give an initial sense of the prevalence of child neurocognitive problems in the form of EF deficits or delays within the Western Cape region, and particularly within rural farm areas. Using the Charan and colleagues (2013) formula regarding the calculation of sample size for a cross-sectional study, the sample size required for the current study was calculated to be N=83, using a confidence interval of 95%, a power of 80% and prevalence of 5.66%. [Calculation: $(1.96)^2 * (0.0566(1-0.0566)) / (0.05)^2 = 83$ (rounded up)] (55).

However, it also important to note that the current study is not solely interested in the effects of maternal gestational drinking on child executive functioning but is also interested in the effects of several other related socio-demographic factors on child executive functioning, which will be modelled. As such it is also important to consider the sample size that would be needed to run such regression models. According to Field (2013), a rule of thumb noted in several textbooks is that to create a reliable regression model one should have 10-15 participants for each predictor included (56).

In the current study, there are ten predictors of interest including: maternal gestational drinking, past maternal drinking, current maternal drinking, household size, parental marital status, home language, maternal employment, maternal education, child gender and child age. To note these predictors will take a categorical format with 2-3 levels (or groups) in the statistical analyses. This means that if we have 10 predictors with a maximum of 3 levels that we should have 30 levels or groups altogether. As such, if we consider having n=10-15 participants for each level of the categorical predictors then a sample size of between N=300 and N=450 is required for the current study.

4.5 Study instruments

4.5.1 Parent and guardian questionnaire

A parent and guardian questionnaire has been created to collect pertinent information about parents or guardians and their children and as such includes several different sections, three of which will be used in the current study (see Appendix 4 & 5). This questionnaire will be translated from English to Afrikaans, and from English to isiXhosa and back translated before use in the field (52). After back translation, the questionnaire will be administered to the parents or guardians of the children participating in the study in their preferred language at their place of residence, with the entire questionnaire being expected to take about an hour to complete (52). Notably, the parent and guardian questionnaire will be administered via an application called Open Data Kit (ODK) using a smart phone. Field workers trained in the administration of the questionnaire and in the use of the ODK software will administer the questionnaire one on one with each mother (or proxy respondent) going through each of the questions on a smart phone, capturing their answers electronically (52).

4.5.1.1 Socio-demographic information

This parent and guardian questionnaire will include several sections, two of which will specifically collect socio-demographic data: the general information section, and the socio-demographic information section (Appendix 4). These two sections will include questions regarding the socio-demographic factors of interest in the current study, including questions regarding: relation of the respondent to the child participant, home language of the parent and child participant, how many people live in the same household as the child participant, the level of education of the mother and father of the child participant, the parents' marital status and the parents' employment status.

4.5.1.2 Information regarding maternal alcohol consumption

Information regarding maternal alcohol consumption before, during and after pregnancy will be collected via the use of the substance use section of the parent and guardian questionnaire (Appendix 5). This section will include questions that have been adapted from previous research studies conducted in the Western Cape (by May et al., 2005 and Katawan et al., 2011) which pertained to mothers alcohol consumption behaviours before, during and after pregnancy (24, 57). Every effort will be made to interview the mother of the child participant, however in cases where the mother is not available questions will be rephrased to ask either the father, grandmother or legal guardian (i.e. a proxy respondent) about the about the biological mother's alcohol consumption behaviours.

4.5.2 Neurocognitive assessment: The CANTAB battery

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is an online application that was developed by a team of neuroscientists at the Cambridge Cognition company for research regarding topics in the fields of neuroscience, neuropsychology and pharmacology (52, 58, 59). The CANTAB includes an array of different neuropsychological tests that tap into several specific cognitive domains (52). Numerous studies have validated the CANTAB, and several studies have shown the CANTAB to be particularly sensitive to variations in children's neuropsychological performance (58-61). Moreover, research has shown that the CANTAB is particularly sensitive to variations in child executive functions due to prenatal alcohol exposure (36, 40).

The CANTAB was used in the current study to assess children's performance on several tasks that tap into various aspects of executive functioning (see Appendix 6). The tasks selected for the CANTAB battery administered to the child participants were those which are known from previous research to tap into key aspects of child executive functioning (36, 40, 61). The aspects of executive functioning (EF) and the selected CANTAB tests tapping into these areas were as follows: [1] *processing speed*, assessed by the motor screening task (MOT) and the reaction time task (RTI), [2] *attention*, assessed by the multi-tasking test (MTT) and the rapid information processing task (RVP), and [3] *memory*, assessed by the spatial working memory task (SWM) and the paired association learning task (PAL).

It is notable that each of these CANTAB subtests result in different key outcome measures, these key outcome measure are fully described in Appendix 7. However, to give a concise description, the key outcomes measured for each of these tests are generally either the number of correct or incorrect responses (hits or misses), or time to response or response failure (in milliseconds) (see Appendix 7 for further details). In the current study, one key outcome measure will be selected to assess performance on each of the CANTAB subtests.

In terms of the administration of the CANTAB battery, field workers went through rigorous training in the use of the CANTAB application which was to be administered via iPads. The CANTAB tests were available in both Afrikaans, English and isiXhosa and children could choose to complete the tests in their preferred language. The CANTAB was administered to a group of 5-7 children at a time, with each group session lasting 35-40 minutes (52). Each child was given their own iPad and earphones to use for the duration of the session. Where possible the CANTAB was administered in a separate, quiet room devoid of distractions. During the session each child sat at a separate desk in a row behind one another, so that they could not view each other's performance.

4.6 Statistical analysis and data management

4.6.1 Statistical analysis plan

Statistical analysis for the current study will be completed using STATA version 14.0 (62). Before any statistical analyses are carried out each of the variables of interest will be examined for noticeable errors, anomalies or missing data, and all variables will be checked for appropriate coding. For the continuous outcome variables, histograms as well as box and whisker plots will be examined to check the normality of the data and transformations will be explored where necessary. On the other hand, to assess the categorical predictor variables, contingency tables will be used to examine the proportions of individuals existing in each category.

After the descriptive statistics have been adequately explored bivariate and multiple regression analyses will be run to examine the influence of each of the ten predictors of interest on the six EF outcomes of interest (one EF outcome variable will be selected for each CANTAB subtest). As the outcomes of interest (performance on the tasks of EF functioning) will be continuous in nature, multiple regression (MR) modelling techniques will be employed. The predictors included in the multiple regression models will be included based on past research, meaning that several predictors will be included in an a priori fashion. Potential confounders known from previous research will be assessed using bivariate analyses, and where significant ($p<0.05$) and will be added to the models.

Altogether, eighteen multiple regression models will be run, with three separate models pertaining to the three different maternal alcohol use behaviours being run for each of the six CANTAB subtest outcomes (i.e. 3*6=18 models). Three separate maternal alcohol use models will be run for each of the CANTAB subtest outcomes as the three maternal alcohol use behaviours are anticipated to be significantly correlated. Altogether, each of the eighteen multiple regression models will regress one maternal alcohol use predictor (past, gestational or current maternal alcohol use) along with the a priori selected socio-demographic variables on each of the six CANTAB subtest EF outcomes.

Table 1: Predictors and their coding

Predictor Variables				
	Predictor Name	**Original Format**	**Response Choices** (Guardian Questionnaire)	**Current study coding** (to be used in statistical analyses)
Potential confounders	Study Area	Categorical	1. Grabouw 2. Piketberg 3. Hex River Valley	0. Hex River 1. Piketberg 2. Grabouw
	Residence (Farm residence?)	Binary	1. Yes 2. No	0. Non-Farm 1. Farm
Maternal alcohol consumption predictors*	Maternal gestational alcohol consumption	Categorical	1. Never 2. Less than 1 glass a day 3. About 1 glass a day 4. More than 1 glass per day	0. No 1. Yes
	Current maternal alcohol consumption	Categorical	1. Never 2. Less than 1 glass a day 3. About 1 glass a day 4. More than 1 glass per day	0. No 1. Yes
	Past maternal alcohol consumption	Categorical	1. Never 2. Less than 1 glass a day 3. About 1 glass a day 4. More than 1 glass per day	0. No 1. Yes
Maternal-specific socio-demographic predictors	Maternal employment	Categorical	1. Yes 2. No 98. Don't Know	0. Employed 1. Unemployed
	Maternal education level	Categorical	0. No schooling 1. Primary education 2. Secondary education 3. Tertiary education	0. ≥ Secondary Education 1. ≤ Primary Education
Child-specific socio-demographic predictors	Child gender	Binary	0. Male 1. Female	0. Female 1. Male
	Child age	Continuous	Months (DoB till CANTAB test date)	0. 9.00 – 10.12 yrs.mnths 1. 11.00 – 12.12 yrs.mnths 2. 13.00 – 15.12 yrs.mnths
General socio-demographic predictors (relating to SES)	Household size	Discrete	Number of members living in same household as the child participant	0. 2-4 members 1. 5-5 members 2. 7+ members
	Parental marital status	Categorical	1. Married/Cohabiting 2. Widowed 3. Divorced/Separated 4. Never married / Never lived together	0. Married 1. Never Married 2. Other
	Home Language	Categorical	1. Afrikaans 2. IsiXhosa 3. English 4. IsiZulu 5. SeSotho 6. IsiNdebele 7. SiSwati 8. Xitsonga 9. Sepedi 10. Tshivenda 11. Setswana 12. Other	0. Afrikaans 1. Non-Afrikaans

*Note: the maternal alcohol consumption predictors were collapsed into binary format, with the 'Never' level being recoded as 'No' meaning no alcohol usage, and the other categories (<1, ≈1, >1 glass/day) being collapsed into 'Yes'

4.6.2 Data management and quality assurance

In line with the overarching pesticide research project the data for the current study will be collected and recorded using and online data capturing software called ODK. Likewise the CANTAB software stores the information collected from child participants on a password protected online server. Having all the data available on secure online servers will allow the researchers to see when and if there are any issues with the data in terms of consistency and completeness. In terms of data collection in the field, each participant will have an envelope with a checklist on the front, to make sure that they have completed each stage of data collection before they leave the data collection venue. To ensure the quality of the data collected, all field workers will receive rigorous training before going out into the field, and regular meetings will be held to update the standard operating procedure (SOP). Questionnaires will be piloted and run-through by the research group to ensure their clarity and coherence.

5. Ethics

It is notable that the current study falls under an ongoing research project that has previously received ethical approval from UCT's Human Research Ethics Committee (HREC reference number: 234/2009, Appendix 8). As the current study will be using previously collected child cognitive data, several ethical procedures have already been carried out. As such, the ethical procedures and considerations described below are largely the same as those used by the ongoing research project that the current study falls under. Notably, the ethical procedures of the ongoing research project (also referred to as the parent study) were carried out in accordance with the ethical guidelines specified by the Declaration of Helsinki of the 25th world Medical Assembly (63). Moreover, as the parent study included potentially vulnerable populations (children) several measures were taken to ensure that the ethical principles of justice, beneficence, non-maleficence and autonomy were upheld at all times throughout the course of data collection.

5.1 Risks and benefits

To ensure that the ethical principles of non-maleficence and beneficence were upheld the parent study aimed to both minimize the risks and maximize the benefits of participation. Although the collection of neurocognitive performance data from child participants study posed minimal physical and psychological risks, precautions were still taken to ensure that all child participants experienced minimal physical discomfort or emotional distress over the course of their participation in these data collection procedures. Notably, similar precautions will be taken with parents and guardians when they are interviewed. Precautions taken when collecting child data included instructing the field workers administering the CANTAB battery to the children to make every effort to respect each participant's feelings and to treat each participant in a respectful manner.

Moreover, during the child assent process, the child participants were informed that they were free to not answer any questions that made them feel uncomfortable and that they were free to withdraw from the study at any time without incurring any consequences. Parent and guardians will be likewise be asked for their consent to participate, and will be told that they can withdraw at any time from being interviewed. In terms of benefits, the findings of the current study have the potential to inform future interventions that could yield benefits for individuals living in the communities in which the study took place. Specifically, the findings of the current study could inform future interventions that address the potential negative effects maternal drinking behaviours have on children's neurocognitive abilities, particularly within rural farming communities in the Western Cape.

5.2 Informed consent process

The parent study of the current research project has previously obtained consent from the Department of Education in the Western Cape (Appendix 1). Additionally, the parent study has received permission to conduct the study from the principals and school boards of six different schools, two from each of the three farming areas (Appendix 2). Once a school granted permission for the study, parents/guardians of learners in grades 4-9 in the school were sent a letter of invitation to participate in the study (Appendix 3). This letter included general information about the study and requested that interested parents give their permission for both themselves and their child to participate. Parents and guardians who provided their permission for participation via the letter of invitation were contacted to arrange a time when they could be visited at their home to complete the informed consent process (Appendix 9). Notably, the parent study provided both English and Afrikaans versions of each of the forms used.

Upon first contact, information regarding the parent study as well as the consent form were read to the parent or legal guardian in the relevant language. Afterwards, all questions regarding the consent form were answered to ensure that the parent or legal guardian fully understood both the procedures and the expectations of the study, after which the parent or legal guardian was asked to sign the consent form (or mark the form with their fingerprint if they could not write). With regards to the participation of children, assent was requested from each child before any testing took place (Appendix 10). It was made clear to all participants (both in the consent and assent forms, as well as verbally) that they were free to withdraw from the study at any time. Moreover, all participants were told that withdrawal from the study or refusal to participate would in no way affect how they would be treated by the study's investigators or the school staff. Notably, no study procedures were performed without the relevant consent and assent forms being signed.

5.3 Privacy and confidentiality

The interviews of the parents and legal guardians will take place in their homes in order to ensure that the interviews remain confidential and also to ensure that the interviews take place in a familiar space where those interviewed are likely to feel most comfortable. One trained field-worker will conduct the interview with one parent or legal guardian and when possible the biological mother will be interviewed. Each interview will be administered using the ODK application to capture the respondents answers electronically. With regards to the child participant's privacy, to keep children's performance on the CANTAB as private as possible arrangements were made with each of the schools to either provide a separate room or room dividers for the testing sessions. Additional arrangements were made with each school to provide every child participating in the CANTAB testing sessions with their own desk. Moreover, the field-worker trained in the administration of the CANTAB was also instructed to place the desks in a line behind one another with all children facing forwards so that they could not view each other's iPad screens.

The parent study has taken several measures to ensure that the information collected from participants has been kept secure and confidential. The hard copy documents that have been collected and filed over the course of the study so far, including the permission, consent and assent forms, are being kept in locked filing cabinets on secure UCT premises. Additionally, each participant in the study has been assigned a unique participant number that was consequently used instead of their name on all of their data collection forms to keep their identity anonymous. The link between each participant name and their participant number is being kept within a password protected electronic list on a secure online academic server, with only the principal researcher having the password to this list. The electronic data sheets which include the data from the CANTAB testing and the data from the ODK application used to interview the parents will also be password protected and kept on secure online servers. Researchers working on this study can access to the CANTAB and ODK electronic data sheets to allow them to perform quantitative data analyses, however it is notable that these data sheets only contain participant numbers and not participant names. With regards to future data disposal, as the parent study is an ongoing longitudinal study, continuing until 2019, disposal of the data will only occur five years after the study has been completed in line with UCT's ethical and legal requirements.

References

1. May PA, Brooke L, Gossage JP, Croxford J, Adnams C, Jones KL, et al. Epidemiology of fetal alcohol syndrome in a South African community in the Western Cape Province. American journal of public health. 2000;90(12):1905.
2. Viljoen DL, Gossage JP, Brooke L, Adnams CM, Jones KL, Robinson LK, et al. Fetal alcohol syndrome epidemiology in a South African community: a second study of a very high prevalence area. Journal of studies on alcohol. 2005;66(5):593-604.
3. May PA, Gossage JP, Marais AS, Adnams CM, Hoyme HE, Jones KL, et al. The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. Drug Alcohol Depend. 2007;88(2-3):259-71.
4. Urban MF, Chersich MF, Fourie L-A, Chetty C, Olivier L, Viljoen D. Fetal alcohol syndrome among grade-one children in the Northern Cape Province: prevalence and risk factors. South African Medical Journal. 2008;98(11):877-82.
5. May PA, de Vries MM, Marais AS, Kalberg WO, Adnams CM, Hasken JM, et al. The continuum of fetal alcohol spectrum disorders in four rural communities in South Africa: Prevalence and characteristics. Drug Alcohol Depend. 2016;159:207-18.
6. Croxford J, Viljoen D. Alcohol consumption by pregnant women in the Western Cape. South African Medical Journal. 1999;89(9).
7. London L. Thedop'system, alcohol abuse and social control amongst farm workers in South Africa: a public health challenge. Social Science & Medicine. 1999;48(10):1407-14.
8. London L. Human rights, environmental justice, and the health of farm workers in South Africa. Int J Occup Environ Health. 2003;9(1):59-68.
9. McKinstry J. Using the past to step forward: fetal alcohol syndrome in the Western Cape Province of South Africa. American Public Health Association; 2005.
10. Conners NA, Bradley RH, Mansell LW, Liu JY, Roberts TJ, Burgdorf K, et al. Children of mothers with serious substance abuse problems: an accumulation of risks. Am J Drug Alcohol Abuse. 2004;30(1):85-100.
11. Keller PS, Cummings EM, Davies PT, Mitchell PM. Longitudinal relations between parental drinking problems, family functioning, and child adjustment. Dev Psychopathol. 2008;20(1):195-212.
12. Knopik VS, Heath AC, Jacob T, Slutske WS, Bucholz KK, Madden PA, et al. Maternal alcohol use disorder and offspring ADHD: disentangling genetic and environmental effects using a children-of-twins design. Psychological medicine. 2006;36(10):1461-71.

13. Jacobson SW, Jacobson JL, Sokol RJ, Chiodo LM, Corobana R. Maternal age, alcohol abuse history, and quality of parenting as moderators of the effects of prenatal alcohol exposure on 7.5-year intellectual function. Alcohol Clin Exp Res. 2004;28(11):1732-45.
14. Corral MM, Holguín SR, Cadaveira F. Neuropsychological characteristics in children of alcoholics: familial density. Journal of Studies on Alcohol. 1999;60(4):509-13.
15. Nigg JT, Glass JM, Wong MM, Poon E, Jester JM, Fitzgerald HE, et al. Neuropsychological executive functioning in children at elevated risk for alcoholism: findings in early adolescence. J Abnorm Psychol. 2004;113(2):302-14.
16. Bernier A, Carlson SM, Whipple N. From external regulation to self-regulation: Early parenting precursors of young children's executive functioning. Child development. 2010;81(1):326-39.
17. Hughes CH, Ensor RA. How do families help or hinder the emergence of early executive function? New Dir Child Adolesc Dev. 2009;2009(123):35-50.
18. Hughes C, Devine RT. For Better or for Worse? Positive and Negative Parental Influences on Young Children's Executive Function. Child development. 2019;90(2):593-609.
19. Mezzacappa E. Alerting, orienting, and executive attention: Developmental properties and sociodemographic correlates in an epidemiological sample of young, urban children. Child development. 2004;75(5):1373-86.
20. Farah MJ, Shera DM, Savage JH, Betancourt L, Giannetta JM, Brodsky NL, et al. Childhood poverty: specific associations with neurocognitive development. Brain Res. 2006;1110(1):166-74.
21. Raver CC, Blair C, Willoughby M. Poverty as a predictor of 4-year-olds' executive function: new perspectives on models of differential susceptibility. Dev Psychol. 2013;49(2):292-304.
22. Blair C, Raver CC. Poverty, stress, and brain development: New directions for prevention and intervention. Academic pediatrics. 2016;16(3):S30-S6.
23. Sarsour K, Sheridan M, Jutte D, Nuru-Jeter A, Hinshaw S, Boyce WT. Family socioeconomic status and child executive functions: The roles of language, home environment, and single parenthood. Journal of the International Neuropsychological Society. 2011;17(1):120-32.
24. Katwan E, Adnams C, London L. Childhood behavioural and developmental disorders. SAMJ: South African Medical Journal. 2011;101(10):724-7.
25. Rochat TJ, Houle B, Stein A, Mitchell J, Bland RM. Maternal alcohol use and children's emotional and cognitive outcomes in rural South Africa. Samj South African Medical Journal. 2019;109(7):526-34.
26. Riley EP, McGee CL. Fetal alcohol spectrum disorders: an overview with emphasis on changes in brain and behavior. Experimental biology and medicine. 2005;230(6):357-65.
27. Riley EP, Infante MA, Warren KR. Fetal alcohol spectrum disorders: an overview. Neuropsychol Rev. 2011;21(2):73-80.

28. Wass TS, Persutte WH, Hobbins JC. The impact of prenatal alcohol exposure on frontal cortex development in utero. Am J Obstet Gynecol. 2001;185(3):737-42.
29. Spadoni AD, McGee CL, Fryer SL, Riley EP. Neuroimaging and fetal alcohol spectrum disorders. Neuroscience & Biobehavioral Reviews. 2007;31(2):239-45.
30. Walker SP, Wachs TD, Gardner JM, Lozoff B, Wasserman GA, Pollitt E, et al. Child development: risk factors for adverse outcomes in developing countries. The lancet. 2007;369(9556):145-57.
31. Walker SP, Wachs TD, Grantham-McGregor S, Black MM, Nelson CA, Huffman SL, et al. Inequality in early childhood: risk and protective factors for early child development. The lancet. 2011;378(9799):1325-38.
32. Jensen SK, Berens AE, Nelson 3rd CA. Effects of poverty on interacting biological systems underlying child development. The Lancet Child & Adolescent Health. 2017;1(3):225-39.
33. Ferguson KT, Cassells RC, MacAllister JW, Evans GW. The physical environment and child development: an international review. Int J Psychol. 2013;48(4):437-68.
34. Kodituwakku PW. Neurocognitive profile in children with fetal alcohol spectrum disorders. Developmental disabilities research reviews. 2009;15(3):218-24.
35. Mattson SN, Goodman AM, Caine C, Delis DC, Riley EP. Executive functioning in children with heavy prenatal alcohol exposure. Alcoholism: Clinical and Experimental Research. 1999;23(11):1808-15.
36. Mattson SN, Roesch SC, Fagerlund Å, Autti-Rämö I, Jones KL, May PA, et al. Toward a neurobehavioral profile of fetal alcohol spectrum disorders. Alcoholism: Clinical and Experimental Research. 2010;34(9):1640-50.
37. Rasmussen C. Executive functioning and working memory in fetal alcohol spectrum disorder. Alcoholism: Clinical and Experimental Research. 2005;29(8):1359-67.
38. Rasmussen C, Bisanz J. Executive functioning in children with fetal alcohol spectrum disorders: profiles and age-related differences. Child Neuropsychology. 2009;15(3):201-15.
39. Rasmussen C, Soleimani M, Pei J. Executive functioning and working memory deficits on the CANTAB® among children with prenatal alcohol exposure. Journal of population therapeutics and clinical pharmacology. 2011;18(1).
40. Green C, Mihic A, Nikkel S, Stade B, Rasmussen C, Munoz D, et al. Executive function deficits in children with fetal alcohol spectrum disorders (FASD) measured using the Cambridge Neuropsychological Tests Automated Battery (CANTAB). Journal of Child Psychology and Psychiatry. 2009;50(6):688-97.
41. Koren G, Nulman I, Chudley AE, Loocke C. Fetal alcohol spectrum disorder. Cmaj. 2003;169(11):1181-5.

42. Chudley AE, Conry J, Cook JL, Loock C, Rosales T, LeBlanc N, et al. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. CMAJ. 2005;172(5 Suppl):S1-S21.
43. Sampson PD, Streissguth AP, Bookstein FL, Little RE, Clarren SK, Dehaene P, et al. Incidence of fetal alcohol syndrome and prevalence of alcohol-related neurodevelopmental disorder. Teratology. 1997;56(5):317-26.
44. Alvik A, Haldorsen T, Groholt B, Lindemann R. Alcohol consumption before and during pregnancy comparing concurrent and retrospective reports. Alcoholism: Clinical and Experimental Research. 2006;30(3):510-5.
45. Sood B, Delaney-Black V, Covington C, Nordstrom-Klee B, Ager J, Templin T, et al. Prenatal alcohol exposure and childhood behavior at age 6 to 7 years: I. dose-response effect. Pediatrics. 2001;108(2):e34-e.
46. Hannigan JH, Chiodo LM, Sokol RJ, Janisse J, Ager JW, Greenwald MK, et al. A 14-year retrospective maternal report of alcohol consumption in pregnancy predicts pregnancy and teen outcomes. Alcohol. 2010;44(7-8):583-94.
47. Banich MT, Compton RJ. Cognitive neuroscience: Cambridge University Press; 2018.
48. Zillmer E, Spiers M, Culbertson W. Principles of neuropsychology: Nelson Education; 2007.
49. Zelazo PD, Carlson SM, Kesek A. The development of executive function in childhood. 2008.
50. Hackman DA, Farah MJ. Socioeconomic status and the developing brain. Trends Cogn Sci. 2009;13(2):65-73.
51. Noble KG, Houston SM, Kan E, Sowell ER. Neural correlates of socioeconomic status in the developing human brain. Dev Sci. 2012;15(4):516-27.
52. 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(1):857.
53. London L, Dalvie M, Cairncross E, Solomon A. The quality of surface and groundwater in the rural Western Cape with regard to pesticides WRC Report No: 795/1/00. Pretoria7 WRC. 2000.
54. Dalvie MA, Cairncross E, Solomon A, London L. Contamination of rural surface and ground water by endosulfan in farming areas of the Western Cape, South Africa. Environmental Health. 2003;2(1):1.
55. Charan J, Biswas T. How to calculate sample size for different study designs in medical research? Indian journal of psychological medicine. 2013;35(2):121.
56. Field A. Discovering statistics using IBM SPSS statistics: sage; 2013.
57. May PA, Gossage JP, Brooke LE, Snell CL, Marais A-S, Hendricks LS, et al. Maternal risk factors for fetal alcohol syndrome in the Western cape province of South Africa: a population-based study. American Journal of Public Health. 2005;95(7):1190-9.

58. Luciana M, Nelson CA. Assessment of neuropsychological function through use of the Cambridge Neuropsychological Testing Automated Battery: performance in 4-to 12-year-old children. Developmental neuropsychology. 2002;22(3):595-624.
59. Roque DT, Teixeira RAA, Zachi EC, Ventura DF. The use of the Cambridge Neuropsychological Test Automated Battery (CANTAB) in neuropsychological assessment: application in Brazilian research with control children and adults with neurological disorders. Psychology & Neuroscience. 2011;4(2):255-65.
60. De Luca CR, Wood SJ, Anderson V, Buchanan J-A, Proffitt TM, Mahony K, et al. Normative data from the CANTAB. I: development of executive function over the lifespan. Journal of clinical and experimental neuropsychology. 2003;25(2):242-54.
61. Goldberg MC, Mostofsky SH, Cutting LE, Mahone EM, Astor B, Denckla MB, et al. Subtle executive impairment in children with autism and children with ADHD. Journal of autism and developmental disorders. 2005;35(3):279-93.
62. LP SLS. College Station, TX: 2015. Stata Statistical Software: Release.14.
63. Association WM. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bulletin of the World Health Organization. 2001;79(4):373.

Appendix 1: Approval letter from Department of Education

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REFERENCE: 20150629-846

ENQUIRIES: Dr A T Wyngaard

Prof Aqiel Dalvie
School of Public Health and Family Medicine
Health Sciences Faculty
Anzio Road
Observatory
7729

Dear Prof Aqiel Dalvie

RESEARCH PROPOSAL: REPRODUCTIVE HEALTH EFFECTS DUE TO PESTICIDE EXPOSURE AMONGST CHILDREN IN THE RURAL WESTERN CAPE IN SOUTH AFRICA

Your application to conduct the above-mentioned research in schools in the Western Cape has been approved subject to the following conditions:

1. Principals, educators and learners are under no obligation to assist you in your investigation.
2. Principals, educators, learners and schools should not be identifiable in any way from the results of the investigation.
3. You make all the arrangements concerning your investigation.
4. Educators' programmes are not to be interrupted.
5. The Study is to be conducted from **20 July 2015 till 30 September 2017**
6. No research can be conducted during the fourth term as schools are preparing and finalizing syllabi for examinations (October to December).
7. Should you wish to extend the period of your survey, please contact Dr A.T Wyngaard at the contact numbers above quoting the reference number?
8. A photocopy of this letter is submitted to the principal where the intended research is to be conducted.
9. Your research will be limited to the list of schools as forwarded to the Western Cape Education Department.
10. A brief summary of the content, findings and recommendations is provided to the Director: Research Services.
11. The Department receives a copy of the completed report/dissertation/thesis addressed to:

    The Director: Research Services
    Western Cape Education Department
    Private Bag X9114
    CAPE TOWN
    8000

We wish you success in your research.

Kind regards.
Signed: Dr Audrey T Wyngaard
Directorate: Research
DATE: 01 July 2015

Appendix 2: Permission letter to school principal and board

Date: _____/______/_______

Dear Principal

Re: An epidemiological cohort study of school-going children investigating reproductive and neurobehavioral effects due to environmental pesticide and cell phone use in the Western Cape, South Africa

We would like to ask for your permission to include Grade 4 – 9 learners at your school in the important study above conducted by the University of Cape Town, Centre for Environmental Health and Occupation Research.

This study will investigate the reproductive and neuro-behavioural health effects that pesticides and radiation from cell-phone usage may have on children. This will be of benefit to people who make use of cell-phones and those exposed to pesticides in the environment that can be absorbed through the skin, breathed in and ingested through contaminated drinking water. The learners will undergo free medical testing and will benefit educationally from participation in the study.

This is a 3-year study, starting in 2017 and ending in 2019. Our sample population is 510 boys and 510 girls from 3 different farmland areas so we will require 340 learners from each area and about ±55 learners from each grade. In the 1st year, the learner will be required to complete a questionnaire at their home on demographic details, health and pesticide exposure and they will be required to perform the following tests at school: produce a urine and blood sample, undergo a physical examination of the genital area; perform a neurobehavioural test on a computer and complete a short questionnaire on pesticide exposure and cellphone use. These tests will be repeated in 2019. The tests will cause minimal disruption as it will last for only 2 hours at most. Additionally, a urine sample will be collected from each learner and a short questionnaire on pesticide exposure administered at school every 3 months during 2017-2019

Participation by your school involves identification of Grade 4-9 classes at the school, making available a copy of the class lists and their birth certificates if possible, distributing letters to all Grade 4-9 parents (copy enclosed) asking them for permission to include their child in the study and arranging an appropriate venue at the school on the days of testing during 2017-2019.

We would like to ensure that you, the learner and their guardian/parent offer your consent to participation before we conduct the study.

The results of the study will help to inform regulations to reduce harmful environmental exposures in residential areas in the Western Cape.

The survey has the approval of the Department of Education and Research Ethics Committee of the University of Cape Town.

Yours sincerely

Signature Removed

Associate Professor MA Dalvie (Principle Investigator)

Cell phone number: 0827863781

Appendix 3: Permission letter for parent

Date: _____/______/_______

Dear Parent/Guardian

Re: An epidemiological cohort study of school-going children investigating reproductive and neurobehavioral effects due to environmental pesticide and cell phone use exposure in the Western Cape, South Africa

We would like to ask for your permission to include your child in the important study above conducted by the University of Cape Town.

This study will investigate the reproductive and neuro-behavioural health effects that pesticides and radiation from cell-phone usage may have on children. This will be of benefit to people who make use of cell-phones and those exposed to pesticides in the environment that can be absorbed through the skin, breathed in and ingested through contaminated drinking water. Your child will undergo free medical testing and will benefit educationally from participation in the study.

This is a 3-year study, starting in 2017 and ending in 2019. In the 1st year, you will be required to complete a questionnaire at your home on your child's demographic details, health and pesticide exposure and your child will be require to perform the following tests at school: produce a urine and blood sample, undergo a physical examination of the genital area; perform a neurobehavioural test on a computer and complete a short questionnaire on pesticide exposure and cellphone use. These tests will be repeated in 2019. The tests will cause minimal disruption as it will last for only 2 hours at most. Additionally, a urine sample will be collected from your child and a short questionnaire on pesticide exposure administered at school every 3 months during 2017-2019.

Please note children at the school will be randomly selected to participate in the study and that your child might not be selected to participate. Can you please indicate in the note attached if you give permission for your child to participate in the study.

The results of the study would help in further planning in reducing environmental exposures in rural areas in the Western Cape. and the impact it has on children's health and development.

The survey has the approval of the Department of Education and Research Ethics Committee of the University of Cape Town.

Yours sincerely

Signature Removed

Associate Professor MA Dalvie (Principle Investigator)

Cell phone number: 0827863781

Appendix 4: General information & socio-demographic information

1. General Information

Introduction: Interviewer Reads to Respondent

This section will focus on general details about the child and his/her family structure for example, where they live and with whom they live.

1.1.	Study ID Number:	
1.2.	Name of child:	
1.3.	Are you the primary caregiver of the **child** or the person most familiar with any health problem(s) the **child** has or had in the past?	☐1 Yes ☐2 No
If answer is "NO" then assess informally whether the person knows enough to complete the questionnaire.		
1.4.	How are you related to the **child**?	☐1 Mother ☐2 Father ☐3 Grandmother ☐4 Grandfather ☐5 Aunt ☐6 Uncle ☐7 Other: **1.4.1. Specify** _____________
1.5.	Study Area:	☐1 Grabouw ☐2 Piketberg ☐3 Hex River Valley
1.6.	Physical address of the household:	
1.7.	Is the household located on the property of a farm?	☐1 Yes ☐2 No
1.8.	If yes (to **1.7.**), what is the name of the farm?	
1.9.	If yes (to **1.7.**), what crops are produced on the farm?	☐1 Apple and pears (stone fruits) ☐2 Table grapes

		☐$_3$ Wine grapes ☐$_4$ Wheat ☐$_5$ Citrus ☐$_6$ Other:**1.9.1. Specify:**____________
1.10.	Name of Interviewer:	☐$_1$ Wisdom ☐$_2$ Phillancia ☐$_3$ Maritza ☐$_4$ Phumla ☐$_5$ Mereldine ☐$_6$ Other: **1.10.1 Specify:** ___________

1.11.	What is the ethnicity of the parent / guardian?	☐$_1$ White ☐$_2$ Mixed Ancenstry ☐$_3$ Black ☐$_4$ Asian
1.12.	What is the ethnicity of the child?	☐$_1$ White ☐$_2$ Mixed Ancestry ☐$_3$ Black ☐$_4$ Asian
1.13.	What is your first / home language?	☐$_1$ Afrikaans ☐$_2$ IsiXhosa ☐$_3$ English ☐$_4$ IsiZulu ☐$_5$ SeSotho ☐$_6$ IsiNdebele ☐$_7$ SiSwati ☐$_8$ Xitsonga

		☐9 Sepedi ☐10 Tshivenda ☐11 Setswana ☐12 Other: **1.13.1 Specify____________**
1.14.	Does the **child** have any biological siblings or biological half-siblings?	☐1 Yes ☐2 No → **go to 2.1**
1.15.	How many brothers and sisters (both biological and half-siblings) does the **child** have?	**1.15.1** |__| Siblings **1.15.2** |__| Half-siblings
1.16.	Please give the ages of your children from the oldest to youngest: **(and indicate with a √ whether they live in this household)**	**1.16.1** 1st – Age |___| **1.16.2** 2nd – Age |___| **1.16.3** 3rd – Age |___| **1.16.4** 4th – Age |___| **1.16.5** 5th – Age |___| **1.16.6** 6th – Age |___| **1.16.7** 7th – Age |___| **1.16.8** 8th – Age |___| **1.16.9** 9th – Age |___| **1.16.10** 10th – Age |___|

2. SOCIO-DEMOGRAPHIC INFORMATION

Introduction: Interviewer Reads to Respondent

This section will focus on questions about work, income and education for the parent and child.

2.1. What is the highest level of education completed by the **child's** mother/female guardian?	☐$_0$ No schooling ☐$_1$ Primary education ☐$_2$ Secondary education ☐$_3$ Tertiary education ☐$_{97}$ N/A
2.2. What is the highest level of education completed by the **child's** father /male guardian?	☐$_0$ No schooling ☐$_1$ Primary education ☐$_2$ Secondary education ☐$_3$ Tertiary education ☐$_{97}$ N/A
2.3. What is the child's mother and father's marital status?	☐$_1$ Married/Cohabiting ☐$_2$ Widowed ☐$_3$ Divorced/Separated ☐$_4$ Never married/Never Lived together
2.4. Has this **child's** mother/ female guardian been employed in the last 12 months?	☐$_1$ Yes ☐$_2$ No
2.5. If yes (to **2.4**), was this long-term/ permanent for 12 months, or contract /seasonal work? *(Choose one)* *(Hint: contract / seasonal work is short-term for only a few months or perhaps they move from one short-term job to another short-term job)*	☐$_1$ Long-term / permanent work **2.5.1.** For how long? ______ (months) ☐$_2$ Contract / seasonal work **2.5.2.** For how long? ______ (months)
2.6. If, yes (to **2.4**), what kind of paid work did the mother/ female guardian do?	☐$_1$ Worked on a farm **2.6.1** Specify crops: ☐$_1$ Apple & pears (stone fruits ☐$_2$ Table grapes ☐$_3$ Wine grapes ☐$_4$ Wheat ☐$_5$ Citrus ☐$_6$ Other: **2.6.1.1 Specify:** __________ ☐$_2$ Worked outside a farm but agricultural **2.6.2** Specify crops: ☐$_1$ Apple & pears (stone fruits ☐$_2$ Table grapes ☐$_3$ Wine grapes ☐$_4$ Wheat ☐$_5$ Citrus ☐$_6$ Other: **2.6.2.1 Specify:** __________ ☐$_3$ Non-farm related ____________________________

2.7. Has this **child's** father/ male guardian been employed in the last 12 months?	☐1 Yes ☐2 No
2.8. If yes (to **2.7**), was this long-term/ permanent for 12 months, or contract /seasonal work? *(Choose one)* *(Hint: contract / seasonal work is short-term for only a few months or perhaps they move from one short-term job to another short-term job)*	☐1 Long-term / permanent work **2.8.1.** For how long? ______ (months) ☐2 Contract / seasonal work **2.8.2.** For how long? ______ (months)
2.9. If, yes (to **2.7**), what kind of paid work did the father/ male guardian do?	☐1 Worked on a farm **2.9.1** Specify crops: ☐1 Apple & pears (stone fruits ☐2 Table grapes ☐3 Wine grapes ☐4 Wheat ☐5 Citrus ☐6 Other: **2.9.1.1 Specify:** __________ ☐2 Worked outside a farm but agricultural **2.9.2** Specify crops: ☐1 Apple & pears (stone fruits ☐2 Table grapes ☐3 Wine grapes ☐4 Wheat ☐5 Citrus ☐6 Other: **2.9.2.1 Specify:** __________ ☐3 Non-farm related ____________________________
Does your **child** do any of the following activities in the field/vineyard/orchard with you or independently?	
2.10. Harvesting crops	☐1 Yes ☐2 No ☐98 Don't Know
2.11. Picking fruit	☐1 Yes ☐2 No ☐98 Don't Know
2.12. Pesticide spraying, mixing or loading	☐1 Yes ☐2 No ☐98 Don't Know

2.13. Cleaning of farm equipment	☐1 Yes ☐2 No ☐98 Don't Know
2.14. Assist in a pesticide store	☐1 Yes ☐2 No ☐98 Don't Know
The following set of questions is on household socio-economic position	
2.15. How many people live in this household?	
2.16. How much money or income does your household receive every month after tax? *(including. money from work, pension, informal business etc.)*	☐0 No income ☐1 R1 – R400 ☐2 R401 – R800 ☐3 R801 – R1600 ☐4 R1601 – R3200 ☐5 R3201 – R6400 ☐6 R6401 – R12800 ☐7 R12801 – R25600 ☐8 25601 or more ☐9 Refused to answer ☐98 Dont know
2.17. Do you or anyone in your household receive any of the following? *(Tick all that apply)*	☐1 Child Support Grant ☐2 Government grant ☐3 State old age pension ☐4 Disability grant ☐5 Care dependency grant ☐6 Foster care grant ☐7 Other: **2.17.1 Specify**________________________

Appendix 5: Alcohol questionnare

9. SUBSTANCE USE

Introduction: Interviewer Reads to Respondent

To understand pesticide exposure, we need to know what other exposures the child may have had. This is a section on the smoking and alcohol exposure that the child may have had before, during and after pregnancy.

HINT: If the biological mother is NOT answering the questions, please phrase them accordingly.

Note: Now I am going to ask you some questions about drinking alcohol		
9.1 Did you (/the mother) drink alcohol during pregnancy?	☐0 Never ☐1 Less than 1 glass a day ☐2 About 1 glass a day ☐3 More than 1 glass a day	
9.2 Do you (/does the mother) currently drink alcohol?	☐0 Never ☐1 Less than 1 glass a day ☐2 About 1 glass a day ☐3 More than 1 glass a day	
9.3 Have you (/has the mother) ever drank alcohol in the past?	☐0 Never **(go to 9.8)** ☐1 Less than 1 glass a day ☐2 About 1 glass a day ☐3 More than 1 glass a day	
Note: FOR QUESTIONS **9.4 – 9.7**: Please, complete the **correct option** as indicated.		
9.4 CURRENT DRINKING: **9.4.1** (*Hint: Question for the mother)* Have you ever felt that you should cut down on your drinking? **9.4.2** (*Hint: Question for the guardian)* Has she (the mother) ever felt that she should cut down on her drinking?	**Mother:** ☐1 Yes ☐2 No ☐98 Do not know	**Guardian:** ☐1 Yes ☐2 No ☐98 Do not know
9.4 PAST DRINKING: **9.4.1** (*Hint: Question for the mother)*	**Mother:** ☐1 Yes	**Guardian:** ☐1 Yes

When you did drink alcohol, did you ever feel that you should cut down on your drinking? **9.4.2** (*Hint: Question for the guardian)* When she (the mother) did drink alcohol, did she ever feel that she should cut down on her drinking?	☐$_2$ No ☐$_{98}$ Do not know	☐$_2$ No ☐$_{98}$ Do not know
9.5 CURRENT <u>DRINKING:</u> **9.5.1** (*Hint: Question for the mother)* Have people annoyed you by criticizing your drinking? **9.5.2** (*Hint: Question for the guardian)* Have people annoyed her (the mother) by criticizing her drinking?	**<u>Mother:</u>** ☐$_1$ Yes ☐$_2$ No ☐$_{98}$ Do not know	**<u>Guardian:</u>** ☐$_1$ Yes ☐$_2$ No ☐$_{98}$ Do not know
9.5 <u>PAST DRINKING:</u> **9.5.1** (*Hint: Question for the mother)* When you did drink alcohol, did people annoy you by criticizing your drinking? **9.5.2** (*Hint: Question for the guardian)* When she (the mother) did drink alcohol, did people annoy her by criticizing her drinking?	**<u>Mother:</u>** ☐$_1$ Yes ☐$_2$ No ☐$_{98}$ Do not know	**<u>Guardian:</u>** ☐$_1$ Yes ☐$_2$ No ☐$_{98}$ Do not know
9.6 CURRENT <u>DRINKING:</u> **9.6.1** (*Hint: Question for the mother)* Have you ever felt bad or guilty about your drinking? **9.6.2** (*Hint: Question for the guardian)* Has she (the mother) ever felt bad or guilty about her drinking?	**<u>Mother:</u>** ☐$_1$ Yes ☐$_2$ No ☐$_{98}$ Do not know	**<u>Guardian:</u>** ☐$_1$ Yes ☐$_2$ No ☐$_{98}$ Do not know
9.6 <u>PAST DRINKING:</u> **9.6.1** (*Hint: Question for the mother)* When you did drink alcohol, did ever feel bad or guilty about your drinking? **9.6.2** (*Hint: Question for the guardian)* When she (the mother) did drink alcohol, did she ever feel bad or guilty about her drinking?	**<u>Mother:</u>** ☐$_1$ Yes ☐$_2$ No ☐$_{98}$ Do not know	**<u>Guardian:</u>** ☐$_1$ Yes ☐$_2$ No ☐$_{98}$ Do not know

9.7 CURRENT <u>DRINKING:</u> **9.7.1** (*Hint: Question for the mother)* Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover? **9.7.2** (*Hint: Question for the guardian)* Has she (the mother) ever had a drink first thing in the morning to steady her nerves or to get rid of a hangover?	**<u>Mother:</u>** ☐1 Yes ☐2 No ☐98 Do not know	**<u>Guardian:</u>** ☐1 Yes ☐2 No ☐98 Do not know
9.7 <u>PAST DRINKING:</u> **9.7.1** (*Hint: Question for the mother)* When you did drink alcohol, did ever have a drink first thing in the morning to steady your nerves or to get rid of a hangover? **9.7.2** (*Hint: Question for the guardian)* When she (the mother) did drink alcohol, did she ever have a drink first thing in the morning to steady her nerves or to get rid of a hangover?	**<u>Mother:</u>** ☐1 Yes ☐2 No ☐98 Do not know	**<u>Guardian:</u>** ☐1 Yes ☐2 No ☐98 Do not know
9.8 Did the mother smoke during pregnancy?	☐0 Never ☐1 Less than 1 cigarette a day ☐2 1-5 cigarettes a day ☐3 6-20 cigarettes a day ☐4 More than a packet a day	
9.9 Does anyone in the household currently smoke or ever smoked at home?	☐0 None ☐1 One ☐2 Two ☐3 More than two	
9.10 Has the mother ever taken any recreational drugs during pregnancy eg: Tik, Marijuana? *(Hint: Interviewer to record the name(s) of the drug(s) used)*	☐1 Never ☐2 Less than 1 times a week ☐3 1-6 times a week ☐4 Once a day ☐5 More than once a day	

Appendix 6: CANTAB subtest descriptions

Table 2. CANTAB Test Descriptions, with permission from Chetty-Mhlanga et al., 2018

	COGNITIVE DOMAIN	TEST	COGNITIVE FUNCTION	OUTCOME	DURATION OF TEST
1	PROCESSING SPEED	Reaction Time (RTI)	Perception of visual stimuli, response to visual stimuli and execution of motor action	movement time, reaction time and response accuracy;	6 minutes
	VISUAL MOTOR INTEGRATION	Motor Screening (MOT)	Sensorimotor/ perceptual motor speed and comprehension difficulties	Time lapse between display to response; number of correct and incorrect responses	2 minutes
2	MEMORY 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	Attention Switching Task (AST)	Attentional set-shifting, cognitive flexibility/ lateralization	Congruency and latency during change of instructions	8 minutes
		Rapid Visual Information Processing (RVP)	Sustained attention and continuous performance, impulse control/inhibition	Sensitivity to target and correct responses	7 minutes

Appendix 7: CANTAB cognitive assessment battery description

Detailed CANTAB subtest descriptions (and outcome measure descriptions)

(1) Reaction Time Task (RTI)
(2) Motor Screening Time Task (MOT)
(3) Multi-tasking Test (MTT)
(4) Rapid Visual Information Processing Task (RVP)
(5) Spatial Working Memory Task (SWM)
(6) Paired Associate Learning Task (PAL)

(1) RTI: Reaction Time

RTI provides assays of motor and mental response speeds, as well as measures of movement time, reaction time and response accuracy.

Task Structure:

In this five-choice reaction time task the subject must press and hold down a touchscreen button at the bottom of the screen.

A yellow spot will appear inside one of five yellow circles at the top of the screen.

Subjects must respond to the spot as quickly as they can by letting go of the button and touching the circle where the yellow spot appeared. This is repeated for 30 trials. Practice trials are available to familiarize subjects with the task.

Cognitive Mechanism:

This test assesses a person's ability to quickly respond to stimuli presentation, thus measuring the time it takes for a person to perceive the stimuli, process the required action, and execute the motor action required. It also allows measurement of anticipatory/ premature responding and perseverative responding.

Task Variant Structure:

Task	Variant	Duration	Task structure
RTI	***Five Choice Practice***	3 minutes	30 trials, practice
RTI	***Five Choice Assessed***	3 minutes	30 trials, assessed
RTI	***Five Choice***	4 minutes	10 trials, practice
			30 trials, assessed
RTI	***Simple and Five-Choice***	6 minutes	10 simple trials, practice (repeated if 3 errors made)
			30 simple trials, assessed
			10 five-choice trials, practice (repeated if 3 errors made)
			30 five-choice trials, assessed

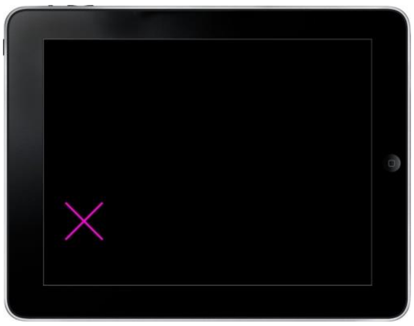
Key Outcome Measures:

Task	Measure Name	Column Header	Description	Mode Applicability
RTI	RTI Median simple reaction time	RTIMDSRT	The median duration between the onset of the stimulus and the time at which the subject released the button. Calculated for correct, assessed trials, in which the stimulus could appear in one location only.	RTI Simple and Five-Choice
RTI	RTI Mean simple movement time	RTIMSMT	The mean time taken to touch the stimulus after the button has been released. Calculated for correct, assessed trials where stimuli could appear in one location only.	RTI Simple and Five-Choice
RTI	RTI Median five-choice reaction time	RTIFMDRT	The median duration between the onset of the stimulus and the release of the button. Calculated for correct, assessed trials where the stimulus could appear in any one of five locations.	RTI Five-Choice RTI Simple and Five-Choice
RTI	RTI Median five-choice movement time	RTIFMDMT	The median time taken to touch the stimulus after the button has been released. Calculated for correct, assessed trials where the stimulus could appear in any one of five locations.	RTI Five-Choice RTI Simple and Five-Choice

(2) MOT – motor screening task

Motor screening provides a general assay of whether sensorimotor or comprehension difficulties limit collecting valid data from the subject

This task tests the learner's motor coordination (ability to use their fine motor and pointing skills) and visual motor integration (see, hear and respond in action) skills. The learner is required to hear the auditory instruction which has been translated into their language preference, and to follow with the visual cues on the iPad.



Task Structure:

The instruction is that a cross will appear on the screen and they have to press on the screen at the exact spot where the cross appears. There are 10 trials before the scores are recorded..

Cognitive Mechanism:

Parameters for this cognitive functioning include the time latency it took from the time of hearing the instruction to the requested action, as well as the accuracy of the participants pointing during the requested action.

Numeric values in milliseconds for reaction time are presented through scores on the mean, median and standard deviation. Percentage scores are presented for accuracy.

Key Outcome Measures:

Task	Measure Name	Column Header	Description	Mode Applicability
MOT	MOTML mean	MOTML	The mean latency from the display of a stimulus to a correct response to that stimulus during assessment trials.	MOT
MOT	MOTTC hits	MOTTC	he total number of assessment trials on which the subject made a correct response.	MOT

(3) MTT: Multi-Tasking Test

MTT is a test of executive function which provides a measure of cued attentional set-shifting.

Task Structure:

On each trial, an arrow appears on the right or on the left hand side of the screen and the participant is asked to make a right or left response.

During training stages, participants learn to either respond according to the direction of the arrow, or according to the side of the screen on which it appears.

During the assessed stage, each trial is preceded by a cue indicating whether the participant should respond according to direction or side. For some trials, the arrow's direction and side are incongruent.

Cognitive Mechanism:

MTT assays two aspects of cognitive flexibility: it allows detection of both a Stroop-like effect (by comparing response latencies and errors from trials in which arrow direction and location are congruent versus incongruent) and a task-switching effect (by comparing response latencies and errors from trial in which participants have to follow the same rule versus a switch rule relative to the previous trial).

Because the task does not depend heavily on novelty, the task is suitable for repeated testing.

Task Variant Structure:

Task	Variant	Duration	Task structure
MTT	***Standard***	8 minutes	8 Direction trials, practice (arrows centred) 8 Direction trials, practice (arrows at sides of screen) 40 Direction trials, assessed 8 Side trials, practice 40 Side trials, assessed 16 Mixed direction & side trials, practice 80 Mixed direction & side trials, assessed

Key Outcome Measures:

Task	Measure Name	Column Header	Description	Mode Applicability
MTT	KEY: MTT Incongruency Cost (Median)	MTTICMD	The difference between the median latency of response (from stimulus appearance to button press) on the trials that were congruent versus the trials that were incongruent. Calculated by subtracting the median congruent latency (in ms) from the median incongruent latency. A positive score indicates that the subject is faster on congruent trials and a negative score indicates that the subject is faster on incongruent trials. A higher incongruency cost indicates that the subjects takes longer to process conflicting information.	MTT Standard
MTT	KEY: MTT Multitasking Cost (Median)	MTTMTCMD	The median latency of response (from stimulus appearance to button press) on congruent trials.	MTT Standard
MTT	KEY: MTT Reaction latency (median)	MTTLMD	The median latency of response (from stimulus appearance to button press). Calculated across all correct, assessed trials.	MTT Standard

(4) RVP: Rapid Visual Information Processing Task

RVP is a sensitive tool for assessment of sustained attention.

Task Structure:

Single digits appear one at a time at a rate of 100 digits per minute. Participants must detect a series of target sequences (e.g. 3-5-7) and touch a button when they see the last digit of a target sequence. Nine target sequences appear every 100 numbers.

Cognitive Mechanism:

This test assesses a person’s ability to hold a target sequence in mind and constantly apply this figure to the stream of numbers presented and calculate if the previous three figures match this sequence. To accomplish this participants must employ sustained attention to process the entire stream of digits being presented.

Performance of RVP has been shown to be associated with activation in a network of brain structures including the frontal and parietal lobes.

Task Variant Structure:

Task	Variant	Duration	Task structure
RVP	***3 Targets***	9 minutes	1 minute practice (with 3-5-7) 6 minutes assessed 3 target sequences: 3-5-7; 2-4-6-; 4-6-8

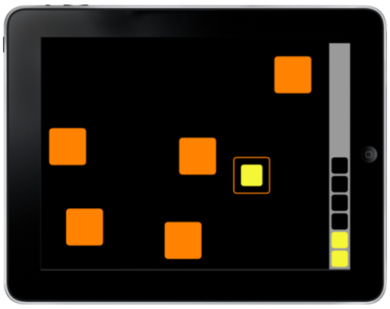
Key Outcome Measures:

Task	Measure Name	Column Header	Description	Mode Applicability
RVP	RVP A’	RVPA	A’ (A prime) is the signal detection measure of sensitivity to the target, regardless of response tendency (the expected range is 0.00 to 1.00; bad to good). In essence, this metric is a measure of how good the subject is at detecting target sequences	RVP 3 Targets RVP 1 Target
RVP	RVP Median response latency	RVPMDL	The median response latency during assessment sequence blocks where the subject responded correctly.	RVP 3 Targets RVP 1 Target

(5) SWM: Spatial Working Memory Task

SWM requires retention and manipulation of visuospatial information. This test has notable executive function demands, and measures strategy use as well as errors.

Task Structure:



The test begins with coloured boxes being shown on the screen. The aim of this test is that, by touching the boxes and using a process of elimination, the subject should find one ‘token’ in each of the boxes and use them to fill up an empty column on the right hand side of the screen.

The key task instruction is that the computer will never hide a token in the same coloured box, so once a token is found in a box the participant should not return to that box to look for another token.

The colour and position of the boxes used are changed from trial to trial to discourage the use of stereotyped search strategies.

Cognitive Mechanism:

This test assesses a person’s ability to retain spatial information and manipulate it in working memory. It is a self-ordered task that also assesses the use of strategy. SWM shows sensitivity to the prefrontal cortex, more specifically the dorsolateral PFC and mid-ventrolateral PFC.

Task Variant Structure:

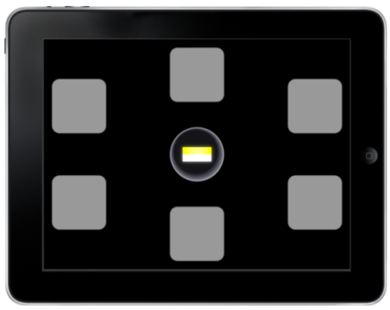
Task	Variant	Duration	Task structure
SWM	***12 Tokens Practice***	6 minutes	3, 6, 9, 12 tokens, practice
SWM	***12 Tokens Assessed***	4 minutes	3 trials of 12 tokens , assessed
SWM	***High Functioning***	9 minutes	3, 6, 9, 12 tokens, practice 12 tokens, assessed
SWM	***Recommended Standard***	5 minutes	2 x 3 token practice trials 4, 6, 8 tokens assessed trials

Key Outcome Measures:

Task	Measure Name	Column Header	Description	Mode Applicability
SWM	SWM Between errors	SWMBE	Between errors are defined as times the subject revisits a box in which a token has previously been found. This is calculated for trials of four, six and eight tokens.	SWM High Functioning SWM Recommdended Standard SWM 12 Tokens Assessed
SWM	SWM Strategy (6-8 boxes)	SWMS	For problems with six boxes or more, the number of distinct boxes used by the subject to begin a new search for a token, within the same problem. (6, 8 tokens)	SWM High Functioning SWM Recommdended Standard SWM 12 Tokens Assessed
SWM	SWM Between errors 4 boxes	SWMBE4	The number of times the subject revisits a box in which a token has previously been found. This is calculated for trials 4 tokens only	SWM Recommended Standard
SWM	SWM Between errors 6 boxes	SWMBE6	The number of times the subject revisits a box in which a token has previously been found. This is calculated for trials 6 tokens only	SWM Recommended Standard
SWM	SWM Between errors 8 boxes	SWMBE8	The number of times the subject revisits a box in which a token has previously been found. This is calculated for trials 8 tokens only	SWM Recommended Standard

(6) PAL: Paired Associates Learning Task

PAL assesses visual memory and new learning and is a sensitive tool for accurate assessment of episodic memory.



Task Structure: Boxes are displayed on the screen and open one by one in a randomized order to reveal patterns hidden inside.

The patterns are then displayed in the middle of the screen, one at a time, and the subject must touch the box where the pattern was originally located.

If the subject makes an error, the patterns are re-presented to remind the subject of their locations. Practice trials with fewer patterns are available to familiarize subjects with the task.

Cognitive Mechanism: This test assesses a person's visuo-spatial episodic memory and is very sensitive to hippocampal function and the integrity of the temporal lobes.

It is a very useful task for assessing patients with questionable dementia, Alzheimer's disease and age-related memory loss.

Task Variant Structure:

Task	Variant	Duration	Task structure
PAL	***12 Patterns Practice***	6 minutes	2, 4, 8, 12 patterns practice (3 attempts)
PAL	***12 Patterns Assessed***	4 minutes	12 patterns assessed (3 attempts)
PAL	***High Functioning***	10 minutes	2, 4, 8, 12 patterns practice (3 attempts) 12 patterns assessed (3 attempts)
PAL	***Recommended Standard***	8 minutes	2 pattern practice 2, 4, 6, 8 patterns assessed (4 attempts)

Key Outcome Measures:

Task	**Measure Name**	**Column Header**	**Description**	**Mode Applicability**
PAL	PAL Total errors (adjusted)	PALTEA	The number of times the subject chose the incorrect box for a stimulus on assessment problems (PALTE), plus an adjustment for the estimated number of errors they would have made on any problems, attempts and recalls they did not reach	All
PAL	PAL First attempt memory score	PALFAMS	The number of correct box choices that were made on the first attempt during assessment problems.	All

Appendix 8: HREC approval

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: sumayah.ariefdien@uct.ac.za

01 June 2009

REC REF: 234/2009

Dr MA Dalvie
Public Health & Family Medicine

Dear Dr Dalvie

PROJECT TITLE: FOLLOW-UP STUDY OF REPRODUCTIVE HEALTH EFFECTS DUE TO ENVIRONMENTAL PESTICIDE EXPOSURE AMONG BOYS IN THE WESTERN CAPE, SOUTH AFRICA.

Thank you for submitting your study to thc Research Ethics Committee for review.

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

Approval is granted for one year till the 05th June 2010.

Please submit an annual progress report if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

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

Please quote the REC. REF in all your correspondence.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

sariefdien

Appendix 9: Caregiver consent form

Consent to participate in a study investigating reproductive and neurobehavioral effects due to environmental pesticide and cell phone use exposure in the Western Cape

1. **Title of research project**

An epidemiological cohort study of school-going children investigating reproductive and neurobehavioral effects due to environmental pesticide and cell phone use exposure in the Western Cape, South Africa

2. **Names of researchers**

   Mohamed Aqiel Dalvie (BSc, Honours, MSc, PhD)

   Wisdom Basera (HBMLS, MPH)

   Shala Mhlanga (BSc (Hons), MSc)

3. **Purpose of the research project**

This study will investigate the reproductive and neuro-behavioural health effects that pesticides and radiation from cell-phone usage may have on children. This study will be of benefit to communities who make use of cell-phone use and those exposed to pesticides in the environment that can be absorbed through the skin, breathed in and ingested through contaminated drinking water. Your child will undergo free medical testing and will benefit educationally from participation in the study.

4. **Description of the research project**

This is a 3-year study, starting in 2017 and ending in 2019. In the 1st year, you will be required to complete a questionnaire at your home on your child's demographic details, health and pesticide exposure and your child will be require to perform the following tests at school: produce a urine and blood sample, undergo a physical examination of the genital area; perform a neurobehavioural test on a computer and complete a short questionnaire on pesticide exposure and cellphone use. These tests will be repeated in 2019. The tests will cause minimal disruption as it will last for only 2 hours at most. Additionally, a urine and hair sample will be collected from your child and a short questionnaire on pesticide exposure administered at school every 3 months during 2017-2019.

The following are more detailed explanations of what each assessment will entail:

a) **Guardian Questionnaire:** A member of our study team will interview you to fill out a ±1hour questionnaire. You will be asked questions about general information about your child, his/her general medical health, genital health history, development, cell-phone usage and lifetime environmental exposure to pesticides.
b) **Urine and hair samples:** Your child has to produce a urine sample (in privacy) voiding into a plastic container and give it to the nurse. The nurse will also draw a few strands of hair or shave a small amount of hair from your child The samples will be analysed for the presence of pesticides.
c) **Blood sample:** A study nurse will draw 10 ml blood from a vein on your child's arm. The blood will be analysed for reproductive hormone levels.
d) **Physical examination:** A nurse will assess your child's reproductive health and development by examining their genital area.
e) **Participant Questionnaire:** A member of our study team will administer a 20-minute questionnaire to your child. It has questions on whether they have a cell-phone and about their experience with using cell-phones and any other technical equipment linked to an internet source. There are a few questions on their leisure activities to determine their exposure to pesticides and electro-magnetic fields (internet etc.) that we are studying.
f) **Behavioural Assessment:** This is a 30-40 minutes assessment to test brain functions like reaction and memory, to be administered by a member of our study team. Your child will be given a tablet, with a program that will ask them to follow instructions and respond through touch-screen, similar to a computer game.

5. **Risks and discomforts of the research**

i. **From the blood tests:** A single needle stick will be felt when the blood is taken. Sometimes a small bruise may occur from the needle stick, but this is minor and will heal quickly. The total amount of blood taken is quite small and the body will quickly replace it. Blood samples will be used only to measure reproductive hormones and will be disposed of at the end of the study.

ii. **From the urine and hair samples:** There will be no discomfort as the urine sample is done privately by the participant themself in the toilet facility. Only a small amount of hair will be collected. The urine and hair sample will only be used to measure any evidence of metabolised pesticides and will be disposed of after this laboratory test.

iii. **From the physical examination:** This examination will have some discomfort for the participant as it requires them to reveal their genital area. However, this exam will be done in a private setting with the use of a curtained zone and in a professional manner by a nurse. In addition the exam is observational and therefore will be done quite briefly.

iv. **From the questionnaires:** There are minimal risks associated with completing the questionnaires. The only risk is a loss of confidentiality about personal information about personal information but the data will be seen only by study personnel. All reports will present data in which individuals will not be identifiable by name but by their study number.

v. **From the behavioural assessment:** There is no risk in completing this assessment. It has been specifically adapted to accommodate children and their ability in this age group.

6. Expected benefits to you and others

i. A doctor/nurse will examine your child's reproductive health.
ii. Refreshments will be provided as compensation for the time spent participating in the study.
iii. This study on the reproductive health effects of pesticides will benefit children living in farming areas and those exposed from the environment. Steps can be taken to reduce or prevent exposure or the pesticides can be selected for further investigation and subsequent banning. The findings from the blood and the urine samples can be used to develop ways in which the amount of pesticides in your body can be monitored in people exposed such as yourself.
iv. The assessment on your child's neurobehavioral status will provide you with information about the child's functioning/coping in their daily activities for school tasks, home tasks and social interaction.

7. Costs from participation in the study.

The study is offered to you at no cost.
In the event a problem is discovered and you wish to be seen by a doctor for it, we can recommend someone for you to see. However, the study cannot pay for these additional medical visits or treatments.

The University of Cape Town (UCT) has insurance cover for the event that research-related injury or harm resulting from your child's participation in the study. The insurer will pay all reasonable medical expenses in accordance with the South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI) in the event of an injury or side effect resulting directly from your participation in the study. You will not be required to prove fault on the part of the University.

The University **will not be liable** for any loss, injuries and/or harm that your child may sustain where the loss is caused by:

The use of unauthorised medicine or substances during the study.

- Any injury that results from your child not following the protocol requirements or the instructions that the study-nurse may give.
- Any injury that arises from inadequate action or lack of action to deal adequately with a side effect or reaction to the study medication.

- An injury that results from negligence on your child's part.

By agreeing to participate in this study, you do not give up your right to claim compensation for injury where you can prove negligence, in separate litigation. In particular, your right to pursue such a claim in a South African court in terms of South African law must be ensured. Note, however, that you will usually be requested to accept that payment made by the University under the SA GCP guideline 4.11 is in full settlement of the claim relating to the medical expenses. An injury is considered study-related if, and to the extent that, it is caused by study activities. You must notify the study nurse immediately of any side effects and/or injuries during the study, whether they are research-related or other related complications.

UCT reserves the right not to provide compensation if, and to the extent that, your child's injury came about because your child chose not to follow the instructions that your child was given while taking part in the study. Your right in law to claim compensation for injury where you prove negligence is not affected.

8. Confidentiality of information collected

Study participants will not be personally identified in any of the study reports. The records will be kept confidential to the extent provided by law. The records, including any identification information, will be destroyed after the data collected has been fully analysed.

9. Documentation of the consent

One copy of this document will be kept together with our research records. A second copy will be given to you to keep.

10. Contact person

You may contact the following persons for answers to further questions about the research, your rights, or any injury you may feel is related to the study:

Principal Investigator: Professor Mohamed Aqiel Dalvie	Telephone #: 021 4066610
Researcher: Mr Wisdom Basera	Telephone #: 082 5802776
Researcher: Mrs Shala Mhlanga	Telephone #: 072 3308540
Ethics Administrator: Lamees Emjedi	Telephone #: 021 4066338

Nature of participation

The participation in this project is voluntary (assent from your child) subsequent to your consent, you may refuse your child to participate or withdraw from the study at any time without penalty or loss of benefits to which you may otherwise be entitled.

Consent of the Parent/Guardian

I have read the information given above. I understand the meaning of this information. I hereby consent my child, ______________________________ to participate in the study.

____________________________ __________________________ _________________________ **Printed**

name of Parent/Guardian **Signature** **Date**

____________________________ _______________________ ______________________

Printed name of Researcher **Signature** **Date**

____________________________ _______________________ ______________________

Printed name of Witness **Signature** **Date**

Date: ______________________

Appendix 10: Child assent form

The Western Cape Pesticides and Cellphone use study

Introduction

Introduction
Hi [child's name]! My name is________________ and I would now like to talk to you about your health. Before I begin, I want to assure you that we have your parent or guardian's permission to approach you. You now have the right to refuse to participate, after I explain to you what we want to do.

1. **Title of research project**
Reproductive and neurobehavioral effects due to environmental pesticide exposure and cell phone use in the Western Cape, South Africa

2. **Purpose of the research**
People have done research on the pesticides that farmers use to protect their crops from insects and how they affect our health. There is very little research done in SA on how these pesticides are harmful to children, so with your help, our study will be one of the very few done so far. Through The University of Cape Town, we are going to be looking at 2 important areas of health that may be affected from being exposed to the pesticides used on the farm and EMF through cell-phone usage. This will help other children living in farming areas who are exposed to pesticides by ensuring that farmers cannot use those harmful chemicals. Pesticides can spread from the environment by the wind that disperses it to drinking water, to skin and may be breathed in. Cell phones are also another area with little research done so far. so we hope to find out more on the effects of mobile phones through this study.

3. **Description of the research project**
This is a 3-year study. The study will be done in the 1st year, 2017 and then again in the 3rd year, 2019. In each of these years, we will need you for one day to do some tests and answer some questionnaires. In between the 2 years, a nurse will visit you every 3 months for a urine sample, hair sample and a short questionnaire on pesticide exposure related activities.

If you agree to participate, you will be asked to complete:

a) Questionnaire:
I want you to know that the answers you give me to the questions I ask about your health and cell phone usage will be private and we won't share your answers with other kids or with your parents. Only project members of this study will see the answers and they will use these answers to help you improve your health. There are no right or wrong answers to these questions I will ask you. We want to know how you feel. Also, if you do not want to answer one particular question or if you want to stop at any time and not answer any more questions, you can do that by telling me you don't want to continue. Nothing will happen to you if you decide not to answer these questions. But your participation is important and will help us understand health problems in children and this will help other children who might have similar health problems in the future. This is a 10-15 minute questionnaire, administered by a member of our study team. It has questions on whether you have a cell-phone and about your experience with using cell-phones and any other technical equipment linked to an internet source.

There are a few questions on your leisure activities to determine your exposure to pesticides and cell phone use (internet etc.) that we are studying.

b) Urine and hair sample: We will collect a urine sample and a hair sample from you to test for chemicals.

c) Blood sample: A nurse will draw a small blood sample from you to check the level of your hormones.

d) Physical examination: A nurse will do a very brief body assessment by examining your genital area.

e) Behavioural Assessment: This is a 30-40 minutes assessment to test your brain functions like reaction and memory, to be administered by a member of our study team. Your will be given a tablet, with a program that will ask you to follow instructions and respond through touch-screen, similar to a computer game.

4. **Confidentiality of information collected**
Your name will not appear in any reports on this study. The records of questionnaires, assessments, blood samples, urine samples and examination, will be kept completely confidential at the University of Cape Town and will be seen only by our study team.

5. **Contact person**.
You may contact one of the following persons for answers to further questions about the research, your rights, or any injury you may feel is related to the study. You may also contact these persons for questions related to your child's rights or any injury you may feel is related to the study.

Principal Investigator: Professor Mohamed Aqiel Dalvie	Telephone #: 021 4066610
Researcher: Mr Wisdom Basera	Telephone #: 082 5802776
Researcher: Mrs Shala Mhlanga	Telephone #: 072 3308540
Ethics Administrator: Lamees Emjedi	Telephone #: 021 4066492

6. **Assent for your participation**
The information above has been read to me. I understand the meaning of this information

Dr./Mr./Ms. ____

has offered to answer any questions concerning the study. By signing this form, I agree to participate in the study. I also understand that I am free to withdraw from the study at any time without penalty.

____________________________________ ______________________________
Printed name of child Signature, Mark, or Thumb Print

____________________________________ _____________________
Interviewer's name (Print) Signature

____________________________________ ______________________________
Witness (Print) Signature

DATE: _____________________

SECTION II: Literature Review

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1. Introduction

Several studies conducted within the Western Cape, South Africa, over the last thirty years have consistently shown inordinately high levels of neurodevelopmental disorders in the form of Fetal Alcohol Syndrome (FAS) and Fetal Alcohol Spectrum Disorders (FASDs) amongst children in this area (1-5). Notably, this research has indicated that the prevalence of FAS and other diagnosable FASD's are increasing. Two consecutive studies conducted in the same area within the Western Cape have shown that the prevalence FAS has risen from 40.5-46.4 per 1000 children in 2000, to 68.0-89.2 per 1000 children in 2007 (1, 3). Moreover, recent research by May and colleagues (2016) within rural lower socio-economic status (SES) areas of the Western Cape has indicated that the prevalence of all FASDs to between 18-26%, indicative of the severity of this issue in this area (1-5).

As such, the issue of maternal alcohol consumption during pregnancy (i.e. prenatally) is becoming an ever more pressing public health problem due to the ramifications that this issue has for early childhood development (ECD) within the Western Cape, and specifically within rural farm areas as a legacy of the 'dop system' (6-10). Within the research conducted in South Africa, maternal gestational drinking has been found to be a strong biological determinant of child neurocognitive outcomes leading to known disorders such as FAS and other diagnosable FASDs (1-5). This local research has also shown that there are several maternal risk factors which act as important socio-demographic determinants of FAS and other diagnosable FASDs (11-13). However, the majority of this research has focused on maternal gestational alcohol use as a biological determinant of diagnoseable FASDs, with little local research also considering the impacts of other forms of maternal drinking behaviours and related socio-demographic factors on the broader spectrum of child neurocognitive outcomes, or on developmentally sensitive neurocognitive outcomes such as child executive functioning (14, 15).

Although there is a lack of local research in this area, there is a growing body of international research indicating that socio-demographic factors, which exist in children's antenatal and postnatal environments, can have significant impacts on several developmentally sensitive aspects of child neurocognitive functioning (16-28). Notably, several international studies have indicated that maternal substance use behaviours before and after pregnancy along with related socio-demographic factors can have a profound influence on child intellectual, behavioural and executive functioning (EF) (16-21). However, as the research conducted within the South African context continues to focus on maternal gestational drinking as a biological determinant of 'full-blown' FAS, there remains a paucity of research examining how other types of maternal alcohol use behaviours (such as those before and after pregnancy) and related socio-demographic factors act as social determinants of the broader spectrum of child neurocognitive functions (14, 15).

As such, this literature review aims to examine the international research regarding the effects of socio-demographic factors on child neurocognitive functioning. Furthermore, this literature review aims to discuss how this international literature, regarding the impacts of socio-demographic factors on sensitive child neurocognitive outcomes, can meaningfully dovetail with the current South African literature regarding the associations between maternal gestational drinking and child FASDs. These two bodies of literature will be examined together in order to determine where and how they meaningfully intersect. Meaningful overlaps between these bodies of literature can add to the current understanding of how biological and socio-demographic factors combine to result in a broader spectrum of child neurocognitive outcomes, and more specifically how these factors come together to negatively impact on developmentally sensitive aspects of child neurodevelopment, such as child EF.

1.1 Outline and objectives

The current literature review has three main overarching objectives: [1] to present and explain key concepts and terminology, [2] to highlight what is presently known from the local research regarding the effects of maternal gestational drinking and other maternal drinking behaviours on developmentally sensitive child neurocognitive outcomes and [3] to underline what is known from international research literature regarding the impacts of different socio-demographic factors on sensitive child neurocognitive outcomes, such as executive functioning.

In order to address these three objectives, the following literature review will be divided into six separate sub-sections. The first section of this literature review aims to provide some contextual background regarding the historical, political and social drivers of child neurocognitive outcomes within South Africa, specifically focusing on the Western Cape. The second section of this literature review aims to clarify the terminology surrounding FASDs and aims to present the issues that come along with diagnosing FASDs. The third section of this literature review aims to present a succinct overview of several key epidemiological studies conducted in South Africa over the past thirty years regarding the effects that maternal alcohol consumption behaviours and other risk factors have on child neurocognitive outcomes. The fourth section aims to discuss how findings regarding the effects of socio-demographic factors on child neurocognitive outcomes from the broader international research literature can be used to inform research conducted in the context of a developing country like South Africa. The fifth section of this literature review aims to clarify what the construct of EF refers to, the biological substrates that have been found to underpin it and how this aspect of neurocognitive functioning is understood to develop across childhood, adolescence and adulthood. Finally, this literature review will conclude by highlighting how the current study will endeavor to combine these concepts and research findings in a meaningful way in order to address the current gaps in local research.

1.2 Search strategy

The literature included in this review was gathered via several consecutive online searches conducted using Google Scholar as the primary search engine. Google Scholar was selected as the primary database for this literature review due to its vast multi-disciplinary scope which fitted well with the topic for this dissertation, which is interdisciplinary in nature. The consecutive online searches conducted were each informed by prior searches, and in some cases where a key article was found the reference section of this article was examined for additional relevant articles. Moreover, several neuropsychological and child development textbooks were consulted. To note, the key search terms for the online searches differed based on the sub-topic being covered: the search terms [Numbered according to the outline above] for each sub-topic included: [1] (child neurocognitive development) AND (developing countries), (child neurocognitive development) AND (South Africa), (Dop System) AND (child health outcomes), [2] (diagnostic criteria for FASD), (neurocognitive profiles of FASD), (executive functioning) AND (FASD), [3] (epidemiological study) AND (Fetal Alcohol Spectrum Disorders) AND (South Africa), (epidemiological study) AND (maternal alcohol consumption behaviours) AND (South Africa), [4] (socio-demographic factors) AND (child neurocognitive outcomes), (adverse environmental factors) AND (child neurocognitive outcomes) and [5] (executive functioning) AND (neural correlates), (executive functioning) AND (child development). The articles collected via the online searches were restricted to articles published in English in peer reviewed journals; articles available in hardcopy were also included. Furthermore, articles published before 1990 were excluded to ensure that the research presented is currently relevant and not outdated.

2. Literature

2.1 Contextual background: The determinants of child neurocognitive outcomes in SA

Although South Africa was democratized in 1994, with the Bill of Rights being introduced into the South African constitution in 1997, the legacy of apartheid has meant that the living and working conditions on many South African farms remains poor (7-9). Specifically, within the rural farm areas of the Western Cape, the additional legacy of the ‘dop system,’ has further impoverished farm workers in this area (7-9, 12). The dop system, initially introduced by Dutch settlers to the Cape in the 1700s, refers to the practice of paying part of farm workers’ wages in unrefined wine, a practice which has continued despite its illegality (7-9, 12). This system has been used to exert control over farm workers, keeping them and their families in an impoverished position over generations through the creation of a culture of alcohol intake and dependence (7-9).

It is notable that although the dop system has had a detrimental impact on the health and well-being of the farm working community in the Western Cape as a whole, this system and the social conditions it has engendered over time continue to have particularly detrimental effects on mothers and their children in this community (7-9).Women constitute around 30% of the workforce on commercial farms and are more than twice as likely than men to be hired as casual labourers with low job security (7-9). Moreover, the low minimum wage in South Africa means that around two thirds of farm-working households live in waged poverty (7-9). Both living in poverty and having low job security impact upon maternal mental health, with research showing that mothers in this region often use alcohol as a coping mechanism to deal with feelings of low self-esteem and depression (7-9). Thus, from current local research it can be argued that social stressors which mothers experience in this local context are likely to have implications for maternal alcohol consumption behaviours before, during and after pregnancy, all of which have the potential to negatively impact on developmentally sensitive child neurocognitive outcomes, such as child EFs (10-15).

In line with this, international research has shown that children's neurocognitive functioning is affected by both biological factors (29-32) and socio-demographic factors (16-28). Notably, recent international research has indicated that specific socio-demographic factors - including socio-economic status (SES), household size, parental employment, maternal education, parental marital status, home language, child gender and child age - each play an important role in the development of sensitive areas of child neurocognitive functioning, such as child intellectual, behavioural and executive functioning (16-18, 22-27, 33). It is also important to note that socio-demographic factors have been shown to play a particularly important role in child neurocognitive outcomes in developing countries, underlining the importance of studying these socio-demographic determinants of child health along with known biological determinants of child health outcomes in the context of a developing country like South Africa (34-37).

2.2 FASDs: Terminology, diagnostic issues & problems surrounding self-report

A diagnosis of FAS requires that, along with evidence of maternal gestational drinking, child-specific symptoms need to be present including: craniofacial dysmorphology, growth restriction and central nervous system (CNS) dysfunction (38-44). However, it is often the case that not all of these symptoms are present in children exposed to alcohol in utero (45). In the past, diagnostic terms including partial FAS (PFAS), fetal alcohol effects (FAE), alcohol related neurodevelopmental disorder (ARND) and alcohol related birth defects (ARBD) have been used to describe individuals who did not display all the required symptoms for FAS (40, 43). However, within the more recent literature, fetal alcohol spectrum disorder (FASD) has been introduced as an umbrella term to encompass all diagnoses and clinical presentations displayed by children exposed to alcohol in utero, acknowledging the spectrum of neurocognitive effects that prenatal alcohol exposure can result in (40, 43). Although the disorders that fall under the umbrella of FASD are diagnostically distinct, it is notable that they share a key feature: neurocognitive dysfunction, and problems with executive functioning in particular (39-43).

As mentioned above, in order to diagnose any disorder that falls within the FASD spectrum (such as FAS, pFAS, FAE, ARND, and ARBD) there needs to be evidence of maternal gestational drinking (45, 46). However, previous research has repeatedly highlighted how difficult it is to diagnose and distinguish between the disorders falling within the FASD spectrum as it is difficult to ascertain whether a child was indeed exposed to alcohol in utero, to what extent they were exposed and for how long they were exposed (45-49). Problems with determining exposure stem from the fact that there is no reliable biological method to detect low to moderate levels of maternal alcohol consumption during pregnancy, which is problematic as research has shown that even low levels of self-reported exposure to alcohol in utero can negatively impact child neurocognitive outcomes (50, 51).

Not having a reliable and objective bio-marker of maternal alcohol use during pregnancy means that researchers are forced to rely largely on self-report measures of maternal gestational alcohol consumption, which are considered unreliable due to response bias and social desirability bias (49, 51). However, more recent research comparing concurrent and retrospective reports of maternal alcohol consumption during pregnancy has suggested that the use of concurrent self-report measures of maternal gestational drinking results in the under-reporting of this behaviour (49), whilst retrospective reports of maternal drinking during pregnancy have been shown to act as better predictors of child health outcomes (51). In light of these research findings, it appears that the use of retrospective self-report may be a more reliable measure of maternal gestational alcohol consumption than previously thought.

2.3 Reviewing recent epidemiological studies conducted in SA regarding maternal drinking

The following table (Table 1a and 1b) present a brief chronological overview of twelve key epidemiological studies conducted in South Africa concerning the associations between maternal drinking behaviours and child neurocognitive outcomes. Each study within Table 1a and 1b are described in terms of study design, sample size, exposures, outcomes and general findings. To note, the majority of these studies were found to examine the associations between maternal *gestational* drinking and child FASDs, with only two recent studies having examined the impacts of non-gestational maternal drinking behaviours on child neurocognitive outcomes (14, 15). The articles described in Table 1a and 1b below were selected by performing two online searches via Google Scholar. The searches conducted using Google Scholar made use of the following Boolean phrases: [1] (epidemiological study) AND (Fetal Alcohol Spectrum Disorders) AND (South Africa), [2] (epidemiological study) AND (maternal alcohol consumption behaviours) AND (South Africa). In terms of criteria for inclusion in the table, the articles selected were peer reviewed articles that were published no more than thirty years ago.

Table 1a. Key epidemiological studies regarding maternal alcohol use behaviours and child neurocognitive outcomes carried out in South Africa over the last 30 years			
Year, Author(s)	**Study Design & Sample Size**	**Exposure(s) & Outcome(s)**	**Study Findings**
1999 Croxford & Viljoen	Descriptive study **N = 636** pregnant woman	***Exposure(s):*** Interviews with pregnant mothers were used to collect information on demographic factors, medical history and personal habits (i.e. substance use). ***Outcome(s):*** The percentage of mothers who were aware of the negative effects of alcohol use during pregnancy on fetal development.	This study found that 42.3% of mothers in their sample admitted to varying degrees of alcohol use during pregnancy, despite 57.1% of the sample reporting that they were aware of the negative effects of alcohol use during pregnancy on fetal development. Overall the study suggested that high rates of alcohol use prevail in poorer communities of the Western Cape province (WC), putting infants in this area at risk for elevated levels of FAS.
2000 May et al	Case ascertainment, Case-control study **N = 626** children, mothers were also interviewed	***Exposure(s):*** Structured maternal interviews were used to collect information on various risk factors including: maternal drinking patterns before, during and after pregnancy, SES indicators and other socio-demographic risk factors. ***Outcome(s):*** Child FAS diagnosis, and child neurocognitive and behavioural functioning using the Griffiths Mental Development Scales (GMDS).	In this study mothers of children with FAS were significantly more likely to report current alcohol use, drinking before pregnancy, and drinking during each trimester of pregnancy than mothers of controls. Moreover, children diagnosed with FAS scored significantly lower on neurocognitive tests than children without FAS. Notably, a high rate of FAS was found in this study sample within in the WC: **40.5 – 46.4 per 1000 children**.
2001 Adnams et al	Case-control study **N = 68** children (34 FAS cases, 34 controls)	***Exposure(s):*** Child FAS diagnosis, controls were matched on age, sex, race and income. ***Outcome(s):*** Performance on various subscales of the Griffiths Mental Development Scales (GMDS), which measure various neurocognitive outcomes.	The results of this study (conducted in the WC) indicated that the group of children with FAS performed significantly worse than the control group on several subscales of the GMDS, specifically: hearing and speech (language), hand-eye co-ordination (fine-motor), performance (pattern construction) and practical reasoning.
2002 Viljoen et al	Case-control study **N = 62** mothers (31 mothers of FAS cases, 31 mothers of controls)	***Exposure(s):*** This study acted as a sub-study of May et al., 2000, using the same structured maternal interviews to collect data about maternal risk factors for FAS. ***Outcome(s):*** Child FAS diagnosis.	This study found that mothers of children with FAS were significantly more likely to report: initiating drinking at an earlier age, current alcohol use, drinking before pregnancy and drinking during each trimester of pregnancy. Mothers of children with FAS also had significantly lower levels of educational attainment and lower levels of religiosity.
2005 Vijoen et al	Case ascertainment, Case-control study **N = 863** children, mothers were also interviewed	***Exposure(s):*** Structured maternal interviews were used to collect information on various risk factors including: maternal drinking patterns before, during and after pregnancy, SES indicators, other socio-demographic risk factors. ***Outcome(s):*** Child FAS diagnosis & child neurocognitive functioning outcomes assessed using Raven's Coloured Progressive Matrices (RCPMs).	This study followed a different birth cohort within the same community within the WC studied by May and colleagues (2000). In this cohort, mothers of children with FAS were significantly more likely to report: current alcohol use, drinking before pregnancy, and drinking during each trimester of pregnancy than mothers of controls. In terms of the neurocognitive tests, a trend was seen, whereby higher reports of alcohol use per day were associated with lower child IQ scores. This study found that the FAS prevalence in this area had risen to **65.2 – 74.2 per 1000 children.**
2005 May et al	Case-control study **N = 170** mothers, (54 mothers of cases, 116 control mothers)	***Exposure(s):*** This study acted as a sub-study of Viljoen et al., 2005, using the same structured maternal interviews to collect data about maternal risk factors for FAS. ***Outcome(s):*** Child FAS diagnosis.	In this study it was found that mothers of children with FAS were significantly more likely to: come from alcohol abusing families themselves, be employed as a farm worker and live in a rural area, compared to mothers of controls. Moreover, compared to mothers of controls, mothers of children with FAS had significantly lower levels of educational attainment, earned significantly less and were significantly more likely to be unmarried but living with a partner.

Table 1b. Key epidemiological studies regarding maternal alcohol use behaviours and child neurocognitive outcomes carried out in South Africa over the last 20 years

Year, Author	Study Design & Sample Size	Exposure(s) & Outcome(s)	Study Findings
2007 May et al	Case ascertainment, Case-control study **N = 218** children, mothers were also interviewed	***Exposure(s):*** Maternal risk data was collected via structured interviews, containing items regarding alcohol, tobacco & drug use before during and after pregnancy, SES indicators, demographic variables, nutrition, mother's physical status and social context. ***Outcome(s):*** Child FAS & PFAS diagnoses & child neurocognitive functioning using RCPMs.	In this study, compared to mothers of controls, mothers of children diagnosed with FAS or PFAS were significantly more likely to: report higher levels of drinking before, during and after pregnancy, to be employed as a farm worker and to live in a rural area. Children with FAS & PFAS were found to score significantly worse on all neurocognitive tests. From this study, conducted within the WC, the joint prevalence of FAS & PFAS was found to be **68.0 – 89.2 per 1000 children.**
2008 May et al	Case-control study **N = 206** mothers, (54 mothers of cases, 134 mothers of controls)	***Exposure(s):*** This study was a sub-study of May et al., 2007, using the same structured maternal interviews to collect data about maternal risk factors for FAS and PFAS. ***Outcome(s):*** Child FAS and PFAS diagnoses.	Within this study, compared to mother of controls, mothers of children diagnosed with FAS or PFAS were significantly more likely to: report current drinking, binge drinking, and drinking during pregnancy, be unmarried but living with a partner, be smaller in stature, have lower levels of educational attainment, and earn less. Notably, compared to children with FAS, children with PFAS displayed lower levels of exposure to the examined maternal risk factors.
2008 Urban et al	Case ascertainment, Case-control study **N=1833** children, mothers were also interviewed	***Exposure(s):*** Structured maternal interviews were carried out to collect data on various maternal risk factors including: demographic variables, SES indicators, and alcohol consumption indicators. ***Outcome(s):*** Child FAS & PFAS diagnosis, and child neurocognitive functioning outcomes using RCPMs.	In this study, compared to mothers of controls, mothers of children with FAS or PFAS were significantly more likely to: have a lower BMI, to be unemployed, to have lower educational attainment, to report current drinking and to report drinking during pregnancy. Moreover, compared to controls, children diagnosed with FAS or PFAS performed significantly worse across all the neurocognitive tests carried out. This study found a prevalence of FAS to be **67.2 per 1000 children** within the community under study in the Northern Cape (NC) Province.
2011 Katwan et al	Case-control study **N = 110** children (55 BDD cases, 55 controls)	***Exposure(s):*** Structured interviews were carried out with the mothers of the cases and controls regarding several maternal risk factors for BDDs, including several questions about different maternal drinking behaviours (before, during and after pregnancy). ***Outcome(s):*** Child neurobehavioural and neurodevelopmental disorders (BDDs).	This study found that compared to mothers of controls, mothers of children with a diagnosed BDD had a significantly higher odds of: drinking 6 months before pregnancy (OR=3.00, CI=1.12-8.03), current alcohol consumption (OR=2.98, CI=1.02-8.70), and having participated in binge drinking in the past 6 moths (OR= 4.67, CI=1.10-19.90), after adjustment.
2016 May et al	Case ascertainment, Case-control study **N=1354** children, mothers were also interviewed	***Exposure(s):*** Structured maternal interviews were carried out to collect data on various maternal risk factors including: demographic variables, SES indicators, and alcohol consumption indicators. ***Outcome(s):*** Child FAS, PFAS and ARND diagnoses and child neurocognitive functioning outcomes using RCPMs.	In this study, compared to mothers of controls, mothers of children with a FASD (FAS, PFAS or ARND) were significantly more likely to: report drinking during pregnancy (at each trimester), report binge drinking, report current drinking, have a lower BMI, have lower level of educational attainment, have less weekly income, and live in a rural area. Moreover, in comparison to controls, children with a diagnosed FASD scored significantly worse across all the neurocognitive tests. This study found the prevalence of **FAS to be 93–128 per 1000 children** and for **all FASDs to be 182 – 259 per 1000 children**.
2019 Rochat et al	Case-control study **N=1505** mothers and **N=1536** children	***Exposure(s):*** Maternal Hazardous Drinking (HD) assessed using the AUDIT. ***Outcome(s):*** Child cognitive, executive functioning and behavioural outcomes, assessed using the KABC-II, NEPSY-II and CBCL (parent-reported) respectively. Information regarding various maternal socio-demographic risk factors were collected in interviews.	Within this study, conducted within Kwazulu-Natal (KZN), it was found that compared to non-HD mothers, mothers who reported HD drinking were significantly more likely to be younger, have lower levels of education and to not be in a current relationship with the child's biological father. Compared to children of non-HD mothers, children of HD mothers were significantly more likely to display poorer outcomes on the cognitive, executive functioning and behavioural assessments.

As can be seen from Table 1a and 1b above, the majority of previous research studies examining the relations between maternal alcohol use behaviours and child neurocognitive outcomes have taken the form of case-control studies. It is also notable that across each of these key epidemiological studies, the methods used have been relatively consistent. The main outcomes examined in these studies are generally one or more diagnosable FASDs (usually full-blown FAS) with children either being classified as cases or controls. Moreover, the information on child exposures in these studies were largely collected through the use of structured interviews conducted with mothers of both cases and controls. Subsequently, follow-up studies using the same data have been conducted after the main study to examine maternal risk factors for different diagnosable FASDs [e.g.: (1) May et al, 2000 and (11) Viljoen et al., 2002].

It is notable that these epidemiological studies have produced consistent results, providing evidence for the high prevalence of FAS and other specific FASD diagnoses in South Africa by both examining the prevalence of these disorders at different times in the same community and at the same time in different communities (1-5). The follow-up studies regarding maternal risk factors have also consistently shown that mothers of children with diagnosed FASD's often display significantly higher odds (or higher probabilities) of having several elevated maternal risk factors (for example: significantly higher levels of binge drinking, current drinking, and higher levels of drinking prior to pregnancy) compared to mothers of control children (i.e. children who do not have a diagnosed FASD) (11-13). One notable trend across this research is that over time there has been an increase in the diagnostic categories within the FASD umbrella examined, with several studies noting the 'spectrum' like effects that maternal gestational alcohol consumption has on child neurocognitive outcomes (1, 3, 5).

However, despite this notable trend there is little local research which focuses on the variations in developmentally sensitive child neurocognitive outcomes such as child EF due to other types of maternal drinking behaviours (which occur before and after pregnancy) and related socio-demographic factors. One recent study by Katawan and colleagues (2011) in the Western Cape found that current maternal drinking (OR=2.98, CI= 1.02-8.70), and past maternal drinking (OR=3.00, CI=1.12-8.03) were both significantly associated with child neurobehavioural and neurodevelopmental disorders (BDDs). Another recent study by Rochat and colleagues (2019), conducted in Kwazulu-Natal, found that children of mothers who reported participating in Hazardous Drinking (HD) behaviours performed significantly worse on tests of cognitive, behavioural and executive functioning. This research provides initial evidence to suggest that other forms of maternal drinking behaviours before and after pregnancy have the potential to negatively impact on developmentally sensitive child neurocognitive outcomes. However, more research is needed to further unpack the impacts of these different forms of maternal alcohol use behaviours along with related socio-demographic risks factors on developmentally sensitive neurocognitive outcomes such as child EF's within the context of South Africa (14, 15).

2.4 Research regarding the biological & socio-demographic determinants of child neurocognitive outcomes

Internationally, there is a considerable body of research which has endeavored to examine the neurocognitive profiles of children diagnosed with specific FASDs (38-44). This international research provides us with important insights regarding maternal gestational alcohol use as a biological determinant of child neurocognitive outcomes (38-44). Notably, this research has repeatedly shown that deficits in child executive functioning (EF) abilities, as displayed by poor performance on EF tasks, acts as a cardinal feature of children exposed to alcohol in utero (41-43). As such, there is a considerable body of research both locally and internationally regarding maternal gestational drinking as a biological determinant of poor child neurocognitive outcomes in the form of FASDs (1-5, 29-32). However, there remains a lack of local and international research which considers the combined impacts of all forms of maternal drinking behaviours (before, during and after pregnancy) and related socio-demographic factors on developmentally sensitive child neurocognitive outcomes (14, 15).

To note, there is a separate body of international research which has shown that several socio-demographic factors also have profound impacts on child neurocognitive outcomes (34-36). This body of research requires further consideration as this research suggests that these socio-demographic factors act as important social determinants of child neurocognitive outcomes and EF outcomes in particular. From this research there is evidence to suggest that child-specific socio-demographic factors (including: child age and child sex gender), maternal-specific socio-demographic factors (including: maternal employment and education level) and general socio-demographic factors (including household size, parental marital status and home language) have profound impacts on child neurocognitive functions and specifically child EF (22-27, 33, 52-59).

In terms of child specific socio-demographic factors, research has shown that older children tend to perform better on EF tasks, and has also shown that boys tend to outperform girls on EF tests of processing speed but that girls outperform boys on tests of working memory (25, 52-55). With regards to maternal specific socio-demographic factors, research has shown that performance on EF tasks is worse for children of unemployed mothers, and children of mothers with lower levels of education (22, 56-58). Lastly, in terms the more general socio-demographic factors, which relate to socio-economic status (SES), research has shown that performance on tests of EF is lower for children who come from larger households with unmarried parents and is also worse for children who do not receive education in their home language (23, 24, 33, 59). Notably, although there is a growing body of international research indicating that socio-demographic factors impact on child EF abilities, there also remains limited research considering the impacts of these factors on child executive functioning within the context of developing countries such as South Africa (34-37).

2.5 Executive Functioning: The construct, biological substrates and the known effects of various biological and socio-demographic factors on its development

Within the neuropsychological research literature, it has been repeatedly emphasized that a specific area of neurocognitive functioning known as executive functioning (EF) is especially sensitive to disruption, both from biological (31, 32) and socio-demographic factors (22-27, 33, 52-59). However, we have yet to discuss what the construct of EF refers to and what biological substrates are understood to underlie this construct (60, 61). As EF is a multifaceted construct, understood to be sub-served by several different functions, this aspect of neurocognitive functioning is difficult to define (60, 61). However, EF can be generally understood to encompass higher order cognitive processes that drive the conscious control of thought and action, generally to realize a goal (60, 62).

The functional capacities contained within the broader EF umbrella are understood to include planning, inhibition, working memory, organized search, set shifting, strategy employment, flexible problem solving, attentional allocation as well as self-monitoring and assessment (60-62). A recent review of several factor analytic studies by Anderson (cited in Zillmer and colleagues, 2008), indicated that there are four main developmentally sensitive areas of EF including: [1] attentional control, [2] information processing, [3] cognitive flexibility and [4] goal setting. From historical neuropsychological cases the frontal cortex of the brain has been determined to be the seat of human EF capabilities, as damage or dysfunction within this area has been shown to lead to poor performance on EF tasks (60-62).

With regards to the development of executive functions (EFs) across the lifespan, although it was initially thought that EFs only emerged during adolescence and adulthood, more recent research has indicated that basic EFs are present during infancy, going on to mature and develop across childhood (61, 62). For example, using the 'hidden object task' developed by Piaget, Diamond (2013) could show that while infants 5-7 months of age did have an understanding of 'object permanence' they did not have the capacity to act on this knowledge, whereas infants aged 7.5-8 months did have the capacity to act on this knowledge (63). This research carried out by Diamond (2013) gives an initial indication that basic aspects of EF are present in infancy, and that they developed steadily and in a progressive fashion as children age (61-63).

Further research has suggested that EFs follow a specific developmental trajectory across childhood. For example, children of 6 years are generally able to perform visual searches (finding a specific target in a complex array of stimuli), children 10 years and above have the capacity to inhibit specific responses, and during adolescence children begin to display complex planning skills and a larger capacity for abstract thinking and problem solving (61, 62). As such, we can see that age plays an important role in the development of EFs: although present from infancy, EFs change, develop and become more complex as children get older (61-63).

It is important to note that unlike many other areas of neurocognitive functioning, EF follows a protracted developmental course through childhood into adolescence, only reaching full maturation during adulthood (61). As such, because EF follows a drawn-out developmental course it is particularly vulnerable to the negative effects of both biological exposures and socio-demographic exposures (61, 62). In terms of harmful biological exposures, research has shown that exposure to alcohol in utero negatively effects the development of the frontal cortex, suggesting a potential explanation for EF problems being a cardinal feature of FASDs (31, 32).

However, there is a growing body of international research which suggests that socio-demographic exposures in the antenatal and postnatal environments also have profound effects on the structure and function of the frontal lobes in children, resulting in EF deficits (28, 64, 65). As such, there is a need for future research in this area to acknowledge and explore how deficits in child EF could in fact be due to a combination between the biological impacts of maternal gestational drinking, and the social impacts of non-gestational maternal drinking behaviours along with related socio-demographic factors.

3. Conclusion: The gaps in the research literature

Within the current literature review two bodies of research considering the impacts of different kinds of factors (biological vs. social) on child neurocognitive outcomes have been highlighted. The first body of literature considered above relates to the impact of maternal gestational alcohol consumption as a biological determinant of poor child neurocognitive outcomes, in the form of FASDs. The other lesser known body of research literature underlined above regards how various socio-demographic factors have been found to act as social determinants of developmentally sensitive child neurocognitive outcomes, such as child EF.

From a biological standpoint, research has shown that maternal alcohol consumption during pregnancy has a particularly detrimental effect on the in-utero development of the central nervous system (CNS), leading to deficits children's neurocognitive functioning (29-32). However, recent research has further suggested that children's neurocognitive functioning is not only affected by direct contact with teratogens such as alcohol during pregnancy but is also affected by past and current maternal alcohol use along with related socio-demographic factors which exist in children's antenatal and postnatal environments (22-27, 33, 52-59).

However, because the impacts of biological and socio-demographic factors on child neurocognitive functioning are generally researched separately, there remains a paucity of research examining how the combined effect of these factors influence developmentally sensitive areas of child neurocognitive functioning, such as child EF. Moreover, there is a particular dearth of research examining both biological and socio-demographic factors and their relative impacts on child neurocognitive outcomes within the context of developing countries, such as South Africa (34-37).

Notably, two recent local research studies have provided initial evidence to suggest that past and current maternal alcohol consumption behaviours are significantly associated with poor child neurocognitive and neurobehavioural outcomes. The first study conducted by Katwan and colleagues (2011) within the Western Cape, found that compared to controls, children with a diagnosed BDD had a significantly higher odds of having a mother who reported drinking 6 months before pregnancy (OR=3.00, CI=1.12-8.03) and had a significantly higher odd of having a mother who reported current drinking (OR=2.98, CI=1.02-8.70). The second study by Rochat and colleagues (2019), conducted in KZN, found that children of mothers who reported participating in hazardous drinking (HD) performed significantly worse on tests of cognitive and executive functioning compared to children of mothers who did not report HD.

These two studies provide initial evidence for the negative impacts of non-gestational maternal drinking behaviours on child neurocognitive outcomes, which requires corroboration through further local research (14, 15). Moreover, the growing body of international research which suggests that socio-demographic factors (including child specific, maternal specific and general SES factors) also have profound effects on child neurocognitive functioning requires additional exploration within the context of a developing country like South Africa (22-27, 33, 52-59). As such, taken together it is apparent that there is a need for further local research to provide a more in-depth understanding of how both biological and socio-demographic factors come together to influence child neurocognitive functioning, and particularly how these factors combine to impact on child EF.

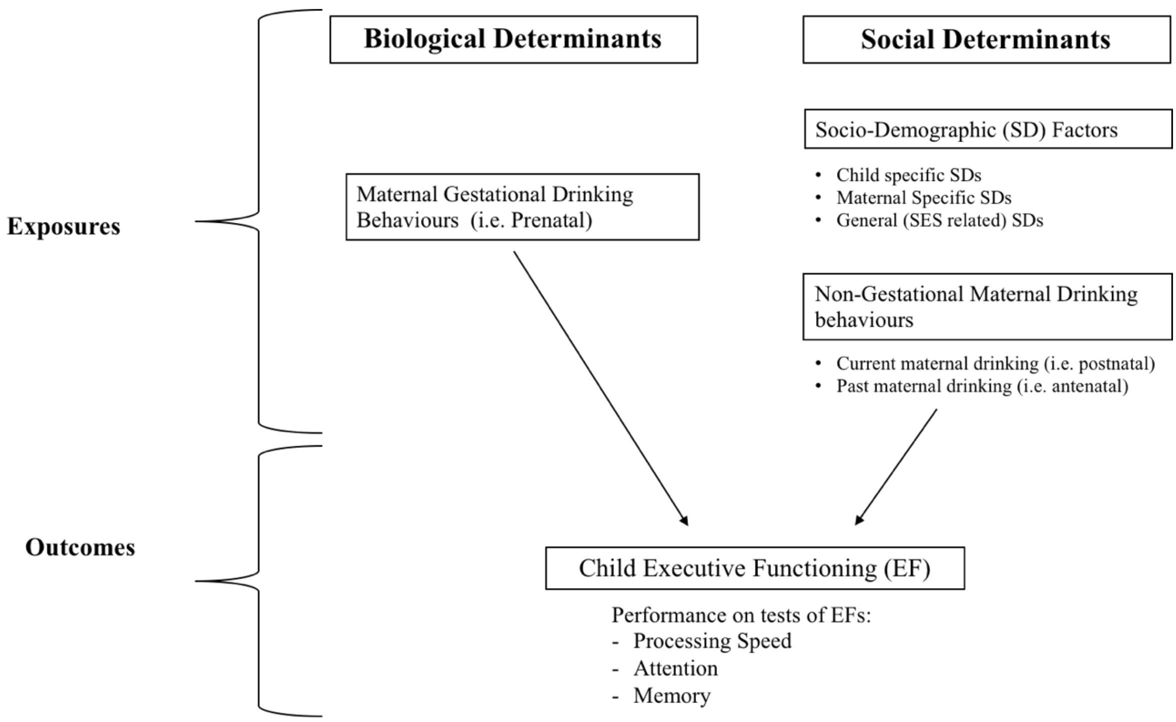

Figure 1. Literature Review - Conceptual Framework

References

1. May PA, Brooke L, Gossage JP, Croxford J, Adnams C, Jones KL, et al. Epidemiology of fetal alcohol syndrome in a South African community in the Western Cape Province. American journal of public health. 2000;90(12):1905.
2. Viljoen DL, Gossage JP, Brooke L, Adnams CM, Jones KL, Robinson LK, et al. Fetal alcohol syndrome epidemiology in a South African community: a second study of a very high prevalence area. Journal of studies on alcohol. 2005;66(5):593-604.
3. May PA, Gossage JP, Marais AS, Adnams CM, Hoyme HE, Jones KL, et al. The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. Drug Alcohol Depend. 2007;88(2-3):259-71.
4. Urban MF, Chersich MF, Fourie L-A, Chetty C, Olivier L, Viljoen D. Fetal alcohol syndrome among grade-one children in the Northern Cape Province: prevalence and risk factors. South African Medical Journal. 2008;98(11):877-82.
5. May PA, de Vries MM, Marais AS, Kalberg WO, Adnams CM, Hasken JM, et al. The continuum of fetal alcohol spectrum disorders in four rural communities in South Africa: Prevalence and characteristics. Drug Alcohol Depend. 2016;159:207-18.
6. Croxford J, Viljoen D. Alcohol consumption by pregnant women in the Western Cape. South African Medical Journal. 1999;89(9).
7. London L. Thedop'system, alcohol abuse and social control amongst farm workers in South Africa: a public health challenge. Social Science & Medicine. 1999;48(10):1407-14.
8. McKinstry J. Using the past to step forward: fetal alcohol syndrome in the Western Cape Province of South Africa. American Public Health Association; 2005.
9. London L. Human rights, environmental justice, and the health of farm workers in South Africa. Int J Occup Environ Health. 2003;9(1):59-68.
10. Adnams CM, Kodituwakku PW, Hay A, Molteno CD, Viljoen D, May PA. Patterns of cognitive-motor development in children with fetal alcohol syndrome from a community in South Africa. Alcoholism: Clinical and Experimental Research. 2001;25(4):557-62.
11. Viljoen D, Croxford J, Gossage JP, Kodituwakku PW, May PA. Characteristics of mothers of children with fetal alcohol syndrome in the Western Cape Province of South Africa: a case control study. Journal of studies on alcohol. 2002;63(1):6-17.
12. May PA, Gossage JP, Brooke LE, Snell CL, Marais A-S, Hendricks LS, et al. Maternal risk factors for fetal alcohol syndrome in the Western cape province of South Africa: a population-based study. American Journal of Public Health. 2005;95(7):1190-9.

13. May PA, Gossage JP, Marais AS, Hendricks LS, Snell CL, Tabachnick BG, et al. Maternal risk factors for fetal alcohol syndrome and partial fetal alcohol syndrome in South Africa: a third study. Alcohol Clin Exp Res. 2008;32(5):738-53.
14. Katwan E, Adnams C, London L. Childhood behavioural and developmental disorders. SAMJ: South African Medical Journal. 2011;101(10):724-7.
15. Rochat TJ, Houle B, Stein A, Mitchell J, Bland RM. Maternal alcohol use and children's emotional and cognitive outcomes in rural South Africa. Samj South African Medical Journal. 2019;109(7):526-34.
16. Conners NA, Bradley RH, Mansell LW, Liu JY, Roberts TJ, Burgdorf K, et al. Children of mothers with serious substance abuse problems: an accumulation of risks. Am J Drug Alcohol Abuse. 2004;30(1):85-100.
17. Keller PS, Cummings EM, Davies PT, Mitchell PM. Longitudinal relations between parental drinking problems, family functioning, and child adjustment. Dev Psychopathol. 2008;20(1):195-212.
18. Knopik VS, Heath AC, Jacob T, Slutske WS, Bucholz KK, Madden PA, et al. Maternal alcohol use disorder and offspring ADHD: disentangling genetic and environmental effects using a children-of-twins design. Psychological medicine. 2006;36(10):1461-71.
19. Jacobson SW, Jacobson JL, Sokol RJ, Chiodo LM, Corobana R. Maternal age, alcohol abuse history, and quality of parenting as moderators of the effects of prenatal alcohol exposure on 7.5-year intellectual function. Alcohol Clin Exp Res. 2004;28(11):1732-45.
20. Corral MM, Holguín SR, Cadaveira F. Neuropsychological characteristics in children of alcoholics: familial density. Journal of Studies on Alcohol. 1999;60(4):509-13.
21. Nigg JT, Glass JM, Wong MM, Poon E, Jester JM, Fitzgerald HE, et al. Neuropsychological executive functioning in children at elevated risk for alcoholism: findings in early adolescence. J Abnorm Psychol. 2004;113(2):302-14.
22. Bernier A, Carlson SM, Whipple N. From external regulation to self-regulation: Early parenting precursors of young children's executive functioning. Child development. 2010;81(1):326-39.
23. Hughes C, Ensor R. How do families help or hinder the emergence of early executive function? New Dir Child Adolesc Dev. 2009;2009(123):35-50.
24. Hughes C, Devine RT. For Better or for Worse? Positive and Negative Parental Influences on Young Children's Executive Function. Child development. 2019;90(2):593-609.
25. Mezzacappa E. Alerting, orienting, and executive attention: Developmental properties and sociodemographic correlates in an epidemiological sample of young, urban children. Child development. 2004;75(5):1373-86.

26. Farah MJ, Shera DM, Savage JH, Betancourt L, Giannetta JM, Brodsky NL, et al. Childhood poverty: specific associations with neurocognitive development. Brain Res. 2006;1110(1):166-74.
27. Raver CC, Blair C, Willoughby M. Poverty as a predictor of 4-year-olds' executive function: new perspectives on models of differential susceptibility. Dev Psychol. 2013;49(2):292-304.
28. Blair C, Raver CC. Poverty, stress, and brain development: New directions for prevention and intervention. Academic pediatrics. 2016;16(3):S30-S6.
29. Riley EP, McGee CL. Fetal alcohol spectrum disorders: an overview with emphasis on changes in brain and behavior. Experimental biology and medicine. 2005;230(6):357-65.
30. Riley EP, Infante MA, Warren KR. Fetal alcohol spectrum disorders: an overview. Neuropsychol Rev. 2011;21(2):73-80.
31. Wass TS, Persutte WH, Hobbins JC. The impact of prenatal alcohol exposure on frontal cortex development in utero. Am J Obstet Gynecol. 2001;185(3):737-42.
32. Spadoni AD, McGee CL, Fryer SL, Riley EP. Neuroimaging and fetal alcohol spectrum disorders. Neuroscience & Biobehavioral Reviews. 2007;31(2):239-45.
33. Sarsour K, Sheridan M, Jutte D, Nuru-Jeter A, Hinshaw S, Boyce WT. Family socioeconomic status and child executive functions: The roles of language, home environment, and single parenthood. Journal of the International Neuropsychological Society. 2011;17(1):120-32.
34. Walker SP, Wachs TD, Gardner JM, Lozoff B, Wasserman GA, Pollitt E, et al. Child development: risk factors for adverse outcomes in developing countries. The lancet. 2007;369(9556):145-57.
35. Walker SP, Wachs TD, Grantham-McGregor S, Black MM, Nelson CA, Huffman SL, et al. Inequality in early childhood: risk and protective factors for early child development. The lancet. 2011;378(9799):1325-38.
36. Jensen SK, Berens AE, Nelson 3rd CA. Effects of poverty on interacting biological systems underlying child development. The Lancet Child & Adolescent Health. 2017;1(3):225-39.
37. Ferguson KT, Cassells RC, MacAllister JW, Evans GW. The physical environment and child development: an international review. Int J Psychol. 2013;48(4):437-68.
38. Kodituwakku PW. Neurocognitive profile in children with fetal alcohol spectrum disorders. Developmental disabilities research reviews. 2009;15(3):218-24.
39. Mattson SN, Goodman AM, Caine C, Delis DC, Riley EP. Executive functioning in children with heavy prenatal alcohol exposure. Alcoholism: Clinical and Experimental Research. 1999;23(11):1808-15.

40. Mattson SN, Roesch SC, Fagerlund Å, Autti-Rämö I, Jones KL, May PA, et al. Toward a neurobehavioral profile of fetal alcohol spectrum disorders. Alcoholism: Clinical and Experimental Research. 2010;34(9):1640-50.
41. Rasmussen C. Executive functioning and working memory in fetal alcohol spectrum disorder. Alcoholism: Clinical and Experimental Research. 2005;29(8):1359-67.
42. Rasmussen C, Bisanz J. Executive functioning in children with fetal alcohol spectrum disorders: profiles and age-related differences. Child Neuropsychology. 2009;15(3):201-15.
43. Rasmussen C, Soleimani M, Pei J. Executive functioning and working memory deficits on the CANTAB® among children with prenatal alcohol exposure. Journal of population therapeutics and clinical pharmacology. 2011;18(1).
44. Green C, Mihic A, Nikkel S, Stade B, Rasmussen C, Munoz D, et al. Executive function deficits in children with fetal alcohol spectrum disorders (FASD) measured using the Cambridge Neuropsychological Tests Automated Battery (CANTAB). Journal of Child Psychology and Psychiatry. 2009;50(6):688-97.
45. Koren G, Nulman I, Chudley AE, Loocke C. Fetal alcohol spectrum disorder. Cmaj. 2003;169(11):1181-5.
46. Chudley AE, Conry J, Cook JL, Loock C, Rosales T, LeBlanc N, et al. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. CMAJ. 2005;172(5 Suppl):S1-S21.
47. Korkman M, Kettunen S, Autti-Ramo I. Neurocognitive impairment in early adolescence following prenatal alcohol exposure of varying duration. Child Neuropsychol. 2003;9(2):117-28.
48. Sampson PD, Streissguth AP, Bookstein FL, Little RE, Clarren SK, Dehaene P, et al. Incidence of fetal alcohol syndrome and prevalence of alcohol-related neurodevelopmental disorder. Teratology. 1997;56(5):317-26.
49. Alvik A, Haldorsen T, Groholt B, Lindemann R. Alcohol consumption before and during pregnancy comparing concurrent and retrospective reports. Alcoholism: Clinical and Experimental Research. 2006;30(3):510-5.
50. Sood B, Delaney-Black V, Covington C, Nordstrom-Klee B, Ager J, Templin T, et al. Prenatal alcohol exposure and childhood behavior at age 6 to 7 years: I. dose-response effect. Pediatrics. 2001;108(2):e34-e.
51. Hannigan JH, Chiodo LM, Sokol RJ, Janisse J, Ager JW, Greenwald MK, et al. A 14-year retrospective maternal report of alcohol consumption in pregnancy predicts pregnancy and teen outcomes. Alcohol. 2010;44(7-8):583-94.
52. Brocki KC, Bohlin G. Executive functions in children aged 6 to 13: A dimensional and developmental study. Developmental neuropsychology. 2004;26(2):571-93.

53. De Luca CR, Wood SJ, Anderson V, Buchanan J-A, Proffitt TM, Mahony K, et al. Normative data from the CANTAB. I: development of executive function over the lifespan. Journal of clinical and experimental neuropsychology. 2003;25(2):242-54.
54. Roalf DR, Gur RE, Ruparel K, Calkins ME, Satterthwaite TD, Bilker WB, et al. Within-individual variability in neurocognitive performance: Age-and sex-related differences in children and youths from ages 8 to 21. Neuropsychology. 2014;28(4):506.
55. Gur RC, Richard J, Calkins ME, Chiavacci R, Hansen JA, Bilker WB, et al. Age group and sex differences in performance on a computerized neurocognitive battery in children age 8− 21. Neuropsychology. 2012;26(2):251.
56. Aran-Filippetti V, Richaud de Minzi MC. A structural analysis of executive functions and socioeconomic status in school-age children: Cognitive factors as effect mediators. The Journal of Genetic Psychology. 2012;173(4):393-416.
57. Ardila A, Rosselli M, Matute E, Guajardo S. The influence of the parents' educational level on the development of executive functions. Developmental neuropsychology. 2005;28(1):539-60.
58. González L, Cortés-Sancho R, Murcia M, Ballester F, Rebagliato M, Rodríguez-Bernal CL. The role of parental social class, education and unemployment on child cognitive development. Gaceta sanitaria. 2018.
59. Rhoades BL, Greenberg MT, Lanza ST, Blair C. Demographic and familial predictors of early executive function development: Contribution of a person-centered perspective. Journal of Experimental Child Psychology. 2011;108(3):638-62.
60. Banich MT, Compton RJ. Cognitive neuroscience: Cambridge University Press; 2018.
61. Zillmer E, Spiers M, Culbertson W. Principles of neuropsychology: Nelson Education; 2007.
62. Zelazo PD, Carlson SM, Kesek A. The development of executive function in childhood. 2008.
63. Diamond A. Executive functions. Annual review of psychology. 2013;64:135-68.
64. Hackman DA, Farah MJ. Socioeconomic status and the developing brain. Trends Cogn Sci. 2009;13(2):65-73.
65. Noble KG, Houston SM, Kan E, Sowell ER. Neural correlates of socioeconomic status in the developing human brain. Dev Sci. 2012;15(4):516-27.

SECTION III: Manuscript

Target Journal: Child Development

Title Page

Maternal alcohol consumption and socio-demographic determinants of neurocognitive function of school children in the rural Western Cape

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Abstract

A cross-sectional study on the impacts of pre, post and gestational maternal alcohol use and related socio-demographic factors on child neurocognitive functions was conducted on children (N=464) within the rural Western Cape in South Africa motivated by limited data on this topic in the country. Testing included the Cambridge Automated Neuropsychological Battery (CANTAB) to assess child executive functioning (EF) and a guardian questionnaire. The study sample was gender balanced and child participants were aged between 9.00-15.12 years.months. Non-significant negative associations were found between maternal drinking behaviours and child EF. Socio-demographic factors including: child age, child sex, home-language, maternal employment, and household-size were found to be significant predictors of subtest specific EF performance, which requires corroboration in future local research.

To date, research conducted in South Africa and specifically within the Western Cape (WC) has shown that the prevalence of Fetal Alcohol Spectrum Disorders (FASDs) are rising (May et al., 2000; May et al., 2016; May et al., 2007). Two consecutive studies by May and colleagues indicated that FAS prevalence in the WC has increased from 40.5-46.4 per 1000 children in 2000 to per 68.0-89.2 per 1000 children in 2007, as compared to an average estimate of 0.97 per 1000 in developed countries (May et al., 2000; May et al., 2007). Moreover, further research by May and colleagues (2016) in rural areas of the WC found the prevalence of FASDs in this area to be between 182-259 per 1000 children, or 18-26%, indicative of the severity of this issue in these rural areas (May et al., 2016).

The high levels 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 these areas, which arguably exist as legacies of both apartheid and the 'dop system,' - the practice of remunerating farm workers with alcohol (Croxford & Viljoen, 1999; London, 1999; May et al., 2005; McKinstry, 2005). More recent local research suggests that maternal alcohol use behaviours follow a particular pattern, whereby maternal drinking begins before pregnancy (antenatally) and continue during pregnancy (prenatally) as well as after pregnancy (postnatally), with each of these behaviours posing a risk for adverse child neurocognitive outcomes (Adnams et al., 2001; Katwan, 2010; Katwan, Adnams, & London, 2011; May et al., 2016; Rochat, Houle, Stein, Mitchell, & Bland, 2019). As such, this local research provides initial evidence to suggest that other forms of maternal alcohol use behaviours (apart from gestational drinking) also have the potential to adversely impact on developmentally sensitive child neurocognitive outcomes, such as child executive function (EF), a finding which requires corroboration through further local research.

Moreover, there is a growing body of international research which indicates that several socio-demographic factors (including: household size, home language, parental marital status, maternal employment, maternal education, child age, and child gender) also have profound effects on child neurocognitive functioning, and on child EF in particular (Aran-Filippetti & Richaud de Minzi, 2012; Gur et al., 2012; C. Hughes & R. T. Devine, 2019; Raver, Blair, & Willoughby, 2013; Sarsour et al., 2011). However, there remains a paucity of research regarding the impacts of the afore mentioned socio-demographic factors on child EF outcomes within the context of lower middle income countries (LMICs) (Ferguson, Cassells, MacAllister, & Evans, 2013; Jensen, Berens, & Nelson 3rd, 2017; Walker et al., 2007; Walker et al., 2011). Therefore, taken together, the evidence from both the local and international research suggests that there is a need to further explore the suggested impacts of different maternal alcohol use behaviours and related socio-demographic factors on developmentally sensitive child neurocognitive outcomes, such as child EF, within the context of a LMIC such as South Africa.

The Current Study

Within South Africa there is limited research regarding the impacts of different forms of maternal alcohol consumption behaviours on child neurocognitive functioning (Katwan, 2010; Katwan et al., 2011; Rochat et al., 2019). Moreover, there is a lack of research regarding the impacts of socio-demographic exposures on developmentally sensitive areas of child neurocognitive functioning, such as child EF. As such, the overarching aim of the current research study was to examine the relative impacts of maternal alcohol use behaviours (including current, gestational and past maternal alcohol use) and related socio-demographic factors (highlighted within previous international research) on developmentally sensitive areas of child neurocognitive functioning, such as child EF.

Based on previous research, several predictions were made regarding the impacts of the different maternal alcohol use behaviours and related socio-demographic exposures on the child EF outcomes that were assessed. Firstly, in terms of the maternal alcohol use behaviours (current, gestational and past maternal alcohol use) it was hypothesized that children of mothers who reported participating in these drinking behaviours would perform significantly worse across all the tasks of EF compared to children of mothers who did not report participating in these drinking behaviours (Adnams et al., 2001; Katwan, 2010; Katwan et al., 2011; Rochat et al., 2019).

In terms of the socio-demographic exposures, these factors were divided into three groups (general, maternal-specific and child-specific socio-demographic factors) in order to facilitate ease of analysis. In terms of the general socio-demographic variables, home language, household size and parental marital status, it was predicted that across the EF subtests performance would be significantly worse for children from larger households, children whose parents were not married, and children whose home language was not the primary language of school instruction (C. Hughes & R. Devine, 2019; Hughes & Ensor, 2009; Raver et al., 2013; Rhoades, Greenberg, Lanza, & Blair, 2011; Sarsour et al., 2011). In terms of the maternal specific socio-demographic factors, it was predicted that performance across the EF subtests would be significantly worse for children of mothers who had only received a primary education (or lower) and children of mothers who were unemployed (Aran-Filippetti & Richaud de Minzi, 2012; Ardila, Rosselli, Matute, & Guajardo, 2005; Bernier, Carlson, & Whipple, 2010; González et al., 2018).

Lastly, in terms of the child-specific socio-demographic factors, it was predicted that child EF performance would significantly differ across child age and sex (Brocki & Bohlin, 2004; De Luca et al., 2003; Roalf et al., 2014). Specifically, based on previous research it was predicted that boys would outperform girls on tests of processing speed, and female children would outperform male children on tests of memory (Gur et al., 2012; Mezzacappa, 2004). Moreover, in terms of child age it was predicted that older children would outperform younger children across all EF subtests (Brocki & Bohlin, 2004; De Luca et al., 2003).

Methods

Participants

The current study is imbedded within the overarching 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 longitudinal study methods have 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 area 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 proxy respondents) of the child participants were interviewed to obtain further information regarding child exposures and pertinent socio-demographic details.

The current study was cross-sectional in design employing data from children (N=1001) tested at schools during a baseline study in 2017 (the last follow-up was conducted in 2019). A sample of N=482 available mothers or proxy respondents were subsequently interviewed at home regarding maternal drinking behaviours and related socio-demographic exposures relevant to developmentally sensitive child neurocognitive outcomes. A further n=18 child participants were removed from the sample based on the exclusion criteria for the current study which included (1) evidence of previous severe child traumatic brain injury (TBI), (2) diagnosed health outcome or pervasive developmental disorder (PDD) known to impact on child neurocognitive functioning and (3) use of prescribed medications known to impact on child neurocognitive performance. As such the final sample for the current study consisted of N=464 children between the ages of 9 to 16 years (see Figure 1).

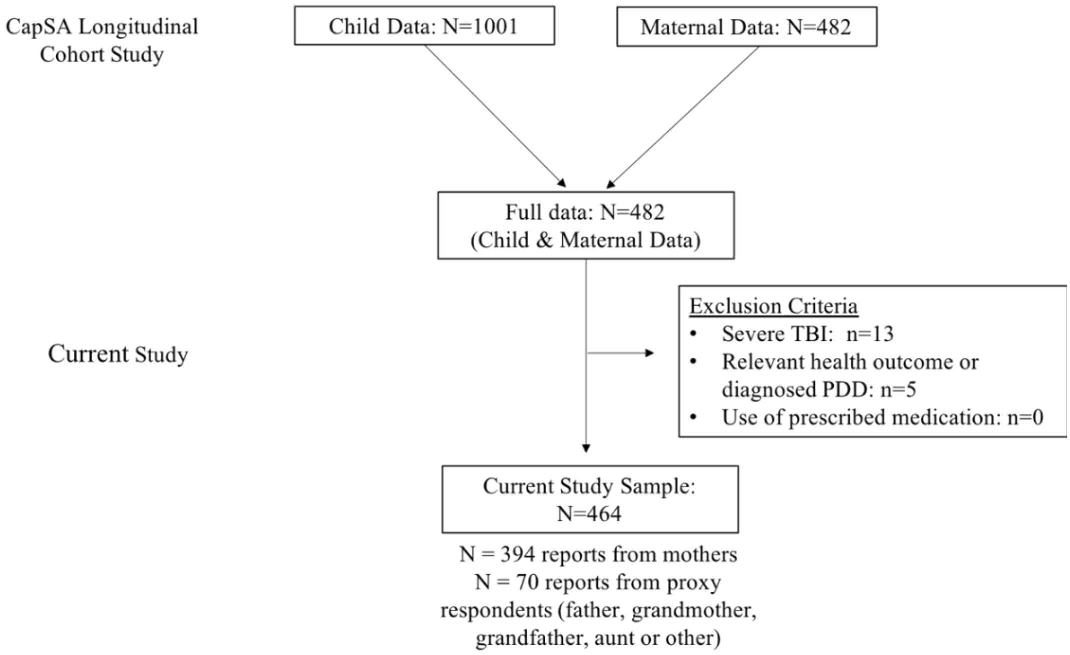

Figure 2. Diagram of sampling and participation in the current study

Procedures

The data from the current study was collected through the overarching CapSA longitudinal cohort study. To note, child assent and parent consent were obtained before any data collection procedures were carried out. More detailed descriptions of the data collection procedures for the overarching CapSA study are available elsewhere (Chetty-Mhlanga et al., 2018). However, the procedures carried out to collect data used in the current study will be briefly highlighted below.

Firstly, in terms of the collection of child data, children 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 was 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 Cambridge Automated Neuropsychological Battery (CANTAB). The CANTAB battery was administered to a group of five to seven children at a time, in their preferred language (Afrikaans, isiXhosa or English), with the testing session lasting between 30 and 45 minutes.

Data from mothers or proxy respondents regarding maternal alcohol use behaviours and related socio-demographic factors was collected via the use of the overarching study's Guardian Questionnaire. The Guardian Questionnaire was administered by trained fieldworkers to mothers or proxy respondents 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 preinstalled on the fieldworkers' mobile phones. The structured interviews with mothers or proxy respondents lasted approximately one hour.

Measures

Outcome Assessment. The primary outcome measure for the current study was the CANTAB, which was used to assess different aspects of child EF 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 (Chetty-Mhlanga et al., 2018; Luciana & Nelson, 2002; Roque, Teixeira, Zachi, & Ventura, 2011).

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 has also shown that the CANTAB can detect subtle impairments in child executive functions (EFs), and has done so in studies across different contexts (Goldberg et al., 2005; Roque et al., 2011).

As such, CANTAB subtests which have been shown to tap into different aspects of EFs were selected for use in the current study (Chetty-Mhlanga et al., 2018). The three different aspects of EF and the CANTAB subtests chosen to assess these aspects of EF were as follows: (1) *processing speed:* assessed using the motor screening test (MOT) and the reaction time task (RTI), (2) *attention:* assessed using the rapid visual information processing task (RVP) and the multi-tasking test (MTT), and (3) *memory:* assessed using the spatial working memory task (SWM) and the paired associates learning (PAL) (see supplement Table A for information regarding the specific outcome measures for each of the CANTAB subtests).

Exposure Assessment. Data regarding the exposures of interest, namely maternal alcohol use behaviours (before, during and after pregnancy) and related socio-demographic factors, was collected via the use of the Guardian Questionnaire. The *general information section* and the *socio-demographic information* section were used to collect information regarding the socio-demographic exposures of interest. Specifically these two sections included questions regarding (1) the general socio-demographic factors of interest: home language, household size, and parental marital status, (2) the maternal specific socio-demographic factors of interest: maternal education and maternal employment and (3) the child specific socio-demographic factors of interest: child age and child sex (see supplement Table B).

Information regarding maternal alcohol use behaviours was collected via the use of the *substance use* section of the Guardian Questionnaire. This section of the questionnaire included questions regarding maternal alcohol use before, during and after pregnancy 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 supplement Table B).

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 alcohol use were purposefully placed near the end of the interview in order to reduce response bias.

Moreover, to increase response rate for the questions about maternal alcohol consumption behaviours, 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). To note, these options were later dichotomised into binary predictors (i.e. [0] No = Never, [1] Yes = <1, ≈1 and >1 glass per day) for the different maternal alcohol use behaviours (see supplement Table B). The dichotomisation of the maternal alcohol use predictors was carried out for two reasons: (1) to be in line with existing local research which has examined different maternal alcohol use behaviours as binary exposures (see Katawan et al., 2011 and Rochat et al., 2019), and (2) the relative frequencies of individuals in each drinking 'frequency' category were low (e.g. for the 9.83% of mothers who reported having participated in gestational alcohol use, 4.15% reported consuming <1 glass per day, 3.49% reported consuming = 1 glass/day, and 2.18% reported that they consumed > 1 glass/day).

Analytic Strategy

Statistical analyses for the current study was completed using Stata 14.0 (StataCorp, 2015). After the exposure variables had been appropriately categorised and the CANTAB subtest EF outcome variables suitably transformed (see supplementary Tables A & B), descriptive univariate and bivariate analyses were carried out to examine the relative frequencies of participants amongst the levels of each of the socio-demographic and maternal alcohol use variables (see Table 1). Moreover, *T-tests* were carried out to determine whether children of self-reported current, gestational or past drinking mothers performed significantly differently from children of self-reported current, gestational or past drinking non-drinking mothers across the EF subtests (see Table 2).

After these initial univariate and bivariate explorations, several multiple regression (MR) models were run in order to explore the impacts of the different maternal alcohol use behaviours and related socio-demographic exposures on child EF outcomes. Altogether, eighteen MR models were run: three separate models pertaining to the three different maternal alcohol use behaviours (gestational, past and current maternal alcohol use) being run for each of the six CANTAB subtest outcomes, which fell into three EF *domains* as follows: (I) *processing speed:* MOTML [tasks/second (t/s)], RTIFMDMT (t/s), (II) *attention*: RVPMDL (t/s), MTTLMD (t/s), (III) *memory:* SWM (hits), (6) PAL (hits) (see supplement Table A). Three separate maternal alcohol use models were run for each CANTAB subtest as the three maternal alcohol use behaviours were highly significantly correlated. As such these maternal alcohol consumption predictors were each separately regressed on the six different CANTAB subtests outcomes along with the all socio-demographic predictors of interest, which were included in the analyses on an a priori basis.

Results

Demographic Information

The descriptive statistics for each of the socio-economic variables (by each of the alcohol use variables) are shown in Table 1. From the total column for current maternal alcohol consumption (for which the whole study sample responded [N=464]), it can be seen that nearly half of the participants were from De Doorns (49.57%) with just over two thirds residing in non-farm areas (69.83%). Afrikaans was the most spoken home language (64.87%), with most children coming from households of more than four members (5-6 members: 38.15%, 7+ members: 23.58 %) in which just over 40% of parents had never married (42.46%). Slightly more than half of the children were female (52.58%), and the youngest age group (9.00-10.12 months years) represented 40.83% of the sample. About 40% (41.59%) of mothers had a primary level of education or lower and more than a third (36.21%) were unemployed. About 10% (9.83%) of mothers reported alcohol consumption during pregnancy, about a third (29.00%) reported current alcohol consumption, and just over a quarter (26.64%) reported past alcohol consumption.

In terms of the bivariate analyses, the relative frequencies of children in each of the socio-demographic variable categories across the self-reported participation in the three maternal alcohol use behaviours can be seen from Table 1's 'yes' columns. In terms of maternal gestational alcohol use, it can be seen that the distributions of children of self-reported drinkers differed somewhat by parental marital status and by maternal education, but was relatively similar for the other socio-demographic factors. For current and past maternal alcohol use, it can be seen that the frequencies of participation in these behaviours did not differ by more than 15% across the levels of the socio-demographic factors, but differed by >15% for study area, home language and parental marital status (see Table 1). Notably, from Table 2 it can be seen that there was no statistically significant differences in the EF subtest performances between self-reported maternal drinkers and non-drinkers across the three maternal drinking behaviours (before, during and after pregnancy).

Multiple Regression Analyses

Processing Speed Subtests: MOT & RTI. None of the models for the MOT subtest were found to be significant overall (see Table 3). However, for the predictor study area it was found that children from Piketberg performed significantly worse (by 10.62-11.50%, calculation: $0.12B$ / $1.13\bar{X}$ [MOT] *100 = 10.62%) than children from De Doorns across all the maternal alcohol use models. Home language was also found to be a significant predictor, with non-Afrikaans speaking children performing significantly worse (by 10.62-11.50%) than Afrikaans speaking children across all the maternal alcohol use models. Non-significant negative associations between each of the maternal alcohol use predictors and MOT subtest performance were observed. In terms of the RTI subtest, all of the models for this subtest were found to be significant overall. Boys significantly outperformed girls (by 10.22-10.45%) across all the maternal alcohol use models and the second oldest child age group (11.00-11.12 years.months) significantly outperformed children from the youngest age group (9.00-9.12 years.months) by 5.45-6.14%. There were non-significant negative associations between the current maternal drinking and gestational maternal drinking predictors and performance on the RTI subtest.

Attention Subtests: RVP & MTT. None of the models for the RVP subtest were found to be significant overall. Moreover, none of the included predictors were found to account for a significant amount of variation in RVP subtest performance. There were non-significant negative associations between each of the maternal alcohol use predictors and performance on the RVP subtest. Conversely, all of the models for the MTT subtest were found to be significant overall. Boys significantly outperformed girls (by 3.79%) and the oldest and second oldest child age groups were found to outperform the youngest age group (by 9.85-10.60% and 8.33% respectively) across all the maternal alcohol use models. Moreover, children of unemployed mothers performed significantly worse (by 3.03-3.82%) compared to children of employed mothers across all the maternal alcohol use models. Non-significant negative associations between the current maternal drinking and gestational maternal drinking predictors and performance on the RTI subtest were seen.

Memory subtests: SWM & PAL. None of the models for the SWM were found to be significant overall. However, it was found that children from households with 5-6 members performed significantly worse (by 8.93-9.29%) than children from households with 2-4 members, across all the maternal alcohol use models. Likewise, none of the models for the PAL subtest were found to be significant overall. Moreover, across all three maternal alcohol use models, none of the included predictors were found to account for a significant amount of variation in performance on the PAL subtest. Non-significant negative associations between current maternal drinking and gestational maternal drinking predictors and performance on the PAL subtest were observed.

Table 1. Sample Demographics for the Predictor variables by the Maternal Alcohol Use Variables

Categorical Predictors	Predictor Levels	Maternal Gestational Alcohol Use			Current Maternal Alcohol Use			Past Maternal Alcohol Use		
		No N (row %)	Yes N (row %)	**Total N (col %)**	No N (row %)	Yes N (row %)	**Total N (col %)**	No N (row %)	Yes N (row %)	**Total N (col %)**
Area	De Doorns	203 (89.43)	24 (10.57)	227 (49.56)	193 (83.91)	37 (16.09)	230 (49.57)	188 (82.82)	39 (17.18)	227 (49.56)
	Piketberg	120 (90.91)	12 (9.09)	132 (28.82)	79 (58.96	55 (41.04)	134 (28.88)	88 (66.67)	44 (33.33)	132 (28.82)
	Grabouw	90 (90.91)	9 (9.09)	99 (21.62)	57 (57.00)	43 (43.00)	100 (21.55)	60 (60.61)	39 (39.39)	99 (21.62)
	Total	**413 (90.17)**	**45 (9.83)**	**458 (100)**	**329 (70.91)**	**135 (29.00)**	**464 (100)**	**336 (73.36)**	**122 (26.64)**	**458 (100)**
Residence	(0) Non-Farm	286 (89.94)	32 (10.06)	318 (68.43)	239 (73.77)	85 (26.23)	324 (69.83)	243 (76.18)	76 (23.82)	319 (69.65)
	(1) Farm	127 (90.71)	13 (9.29)	140 (30.57)	90 (64.29)	50 (35.71)	140 (30.17)	93 (66.91)	46 (33.09)	139 (30.35)
	Total	**413 (90.17)**	**45 (9.83)**	**458 (100)**	**329 (70.91)**	**135 (29.00)**	**464 (100)**	**336 (73.36)**	**122 (26.64)**	**458 (100)**
Home Language	(0) Afrikaans	266 (89.26)	32 (10.74)	298 (65.07)	186 (61.79)	115 (38.21)	301 (64.87)	201 (67.45)	97 (32.55)	298 (65.07)
	(1) Non-Afrikaans	147 (91.88)	13 (8.12)	160 (34.93)	143 (87.73)	20 (12.27)	163 (35.13)	135 (84.38)	25 (15.62)	160 (34.93)
	Total	**413 (90.17)**	**45 (9.83)**	**458 (100)**	**329 (70.91)**	**135 (29.00)**	**464 (100)**	**336 (73.36)**	**122 (26.64)**	**458 (100)**
Parental Marital Status	(0) Married	172 (92.97)	13 (7.03)	185 (40.39)	143 (76.06)	45 (23.94)	188 (40.52)	129 (69.35)	57 (20.65)	186 (40.61)
	(1) Never Married	171 (87.69)	24 (12.31)	195 (42.58)	139 (70.56)	58 (29.44)	197 (42.46)	156 (80.41)	38 (19.59)	194 (42.36)
	(2) Other	70 (89.74)	8 (10.26)	78 (17.03)	47 (59.49)	32 (40.51)	79 (17.03)	51 (65.38)	27 (34.62)	78 (17.03)
	Total	**413 (90.17)**	**45 (9.83)**	**458 (100)**	**329 (70.91)**	**135 (29.00)**	**464 (100)**	**336 (73.36)**	**122 (26.64)**	**458 (100)**
Household Size	2-4 members	163 (93.68)	11 (6.32)	174 (37.99)	132 (74.58)	45 (25.42)	177 (38.15)	136 (77.71)	39 (22.29)	175 (38.21)
	5-6 members	150 (85.23)	26 (14.77)	176 (38.43)	122 (68.93)	55 (31.07)	177 (38.15)	126 (72.00)	49 (28.00)	175 (38.21)
	7+ members	100 (92.59)	8 (7.41)	108 (23.58)	75 (68.18)	35 (31.82)	110 (23.71)	74 (68.52)	34 (31.48)	108 (23.58)
	Total	**413 (90.17)**	**45 (9.83)**	**458 (100)**	**329 (70.91)**	**135 (29.00)**	**464 (100)**	**336 (73.36)**	**122 (26.64)**	**458 (100)**
Child Sex	(0) Female	217 (90.42)	23 (9.58)	240 (52.40)	180 (73.77)	64 (26.23)	244 (52.58)	173 (72.38)	66 (27.62)	239 (52.18)
	(1) Male	196 (89.91)	22 (10.09)	218 (47.60)	149 (67.73)	71 (32.27)	220 (47.41)	163 (74.43)	56 (25.57)	219 (47.82)
	Total	**413 (90.17)**	**45 (9.83)**	**458 (100)**	**329 (70.91)**	**135 (29.00)**	**464 (100)**	**336 (73.36)**	**122 (26.64)**	**458 (100)**
Child Age	(0) 9.0-10.12	172 (91.28)	15 (8.02)	187 (40.83)	130 (68.42)	60 (31.58)	190 (40.95)	131 (69.68)	57 (30.32)	188 (41.05)
	(1) 11.0-12.12	135 (87.66)	19 (12.34)	154 (33.62)	106 (67.95)	50 (32.05)	156 (33.62)	112 (72.73)	42 (27.27)	154 (33.62)
	(2) 13.0-15.12	106 (90.60)	11 (9.40)	117 (25.55)	93 (78.81)	25 (21.19)	118 (25.43)	93 (80.17)	23 (19.83)	116 (25.32)
	Total	**413 (90.17)**	**45 (9.83)**	**458 (100)**	**329 (70.91)**	**135 (29.00)**	**464 (100)**	**336 (73.36)**	**122 (26.64)**	**458 (100)**
Maternal Education	(1) $\geq$ Secondary	250 (92.94)	19 (7.06)	269 (58.73)	185 (68.27)	86 (31.73)	271 (58.41)	195 (72.49)	74 (27.51)	269 (58.73)
	(0) $\leq$ Primary	163 (86.24)	26 (13.76)	189 (41.27)	144 (74.61)	49 (25.39)	193 (41.59)	141 (74.60)	48 (25.40)	189 (41.27)
	Total	**413 (90.17)**	**45 (9.83)**	**458 (100)**	**329 (70.91)**	**135 (29.00)**	**464 (100)**	**336 (73.36)**	**122 (26.64)**	**458 (100)**
Maternal Employment	(0) Employed	261 (88.78)	33 (11.22)	294 (64.19)	209 (70.61)	87 (29.39)	296 (63.79)	218 (74.15)	76 (25.85)	294 (64.19)
	(1) Unemployed	152 (92.68)	12 (7.32)	164 (35.81)	120 (71.43)	48 (28.57)	168 (36.21)	118 (71.95)	46 (28.05)	164 (35.81)
	Total	**413 (90.17)**	**45 (9.83)**	**458 (100)**	**329 (70.91)**	**135 (29.00)**	**464 (100)**	**336 (73.36)**	**122 (26.64)**	**458 (100)**

Table 2. Sample Demographics for the Outcome variables by the Maternal Alcohol Use Variables

CANTAB Subtest	CANTAB Outcomes	Maternal Gestational Alcohol Use				Current Maternal Alcohol Use				Past Maternal Alcohol Use			
		No $\bar{X}$(SD)	Yes $\bar{X}$(SD)	P Value *T-test*	**Total** $\bar{X}$(SD)	No $\bar{X}$(SD)	Yes $\bar{X}$(SD)	P Value *T-test*	**Total** $\bar{X}$(SD)	No $\bar{X}$(SD)	Yes $\bar{X}$(SD)	P Value *T-test*	**Total** $\bar{X}$(SD)
MOT	MOTML	1.13 (0.38)	1.09 (0.44)	0.480	**1.13 (0.39)**	1.13 (0.40)	1.11 (0.37)	0.664	**1.13 (0.39)**	1.13 (0.39)	1.11 (0.38)	0.573	**1.13 (0.39)**
RTI	RTIFMDMT	4.41 (0.99)	4.32 (1.12)	0.584	**4.40 (1.01)**	4.37 (0.99)	4.42 (1.06)	0.605	**4.39 (1.01)**	4.37 (0.97)	4.47 (1.09)	0.371	**4.40 (1.01)**
RVP	RVPMDL	2.44 (0.70)	2.34 (0.59)	0.361	**2.43 (0.69)**	2.46 (0.71)	2.36 (0.64)	0.144	**2.43 (0.69**	2.44 (0.71)	2.38 (0.65)	0.430	**2.43 (0.69)**
MTT	MTTLMD	1.32 (0.22)	1.31 (0.19)	0.947	**1.32 (1.21)**	1.32 (0.22)	1.31 (0.20)	0.888	**1.32 (0.21)**	1.32 (0.21)	1.32 (0.21)	0.901	**1.32 (0.21)**
SWM	SWMBE	13.89 (5.46)	13.88 (5.07)	0.995	**13.89 (5.42)**	13.80 (5.24)	14.08 (5.78)	0.611	**13.88 (5.40)**	13.87 (5.51)	13.97 (5.17)	0.862	**13.89 (5.42)**
PAL	PALFAMS	11.53 (4.22)	11.24 (5.01)	0.673	**11.50 (4.30)**	11.61 (4.36)	11.13 (4.22)	0.279	**11.47 (4.22)**	11.51 (4.37)	11.49 (4.14)	0.975	**11.50 (4.30)**

*p<.05

Table 3. The MR relations between the predictors and the performance on each of the CANTAB Subtests

	EF domain (units)	**Processing Speed** (tasks/second)						**Attention** (tasks/second)						**Memory** (hits)					
	CANTAB Subtest	**MOT**			**RTI**			**RVP**			**MTT**			**SWM**			**PAL**		
	Model #	1 (G)[a]	2 (C)	3 (P)	4 (G)	5 (C)	6 (P)	7 (G)	8 (C)	9 (P)	10 (G)	11 (C)	12 (P)	13 (G)	14 (C)	15 (P)	16 (G)	17 (C)	18 (P)
Categorical Predictor	Category Coefficients	*B*[b]	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*B*
Constant	Intercept	**1.28****	**1.28****	**1.29****	**3.98****	**3.99****	**3.96****	**2.36****	**2.37****	**2.36****	**1.23****	**1.23****	**1.23****	**14.61****	**14.47****	**14.48****	**11.91****	**11.87****	**11.87****
Area	De Doorns																		
	Piketberg	**-.13***	**-.12***	**-.13***	.14	.15	.14	.01	.05	.02	.02	.03	.02	-1.22	-1.33	-1.28	-1.30	-1.11	-1.28
	Grabouw	-.02	-.01	-.01	.29	.32	.28	.05	.07	.05	.04	.04	.04	-.51	-.69	-.60	.37	.50	.37
Residence	Non-Farm																		
	Farm	.01	.01	.01	-.16	-.14	-.15	-.00	-.00	.01	.03	.03	.03	.56	.55	.56	-.63	-.59	-.61
Home Language	Afrikaans																		
	Non-Afrikaans	**-.12***	**-.13***	**-.12***	-.09	-.09	-.08	.14	.14	.14	-.01	-.01	-.01	.02	.04	.04	-.73	-.89	-.68
Parental Marital Status	Married																		
	Never Married	-.08	-.08	**-.09***	.13	.15	.12	.01	.03	.01	.02	.03	.02	.45	.39	.50	-.13	-.11	-.15
	Other	-.06	-.07	-.06	.23	.26	.22	.04	.05	.04	.02	.03	.02	.07	.02	.09	.23	.11	.23
Household Size	2-4 Members																		
	5-6 Members	.01	.01	.01	-.02	-.01	-.03	-.11	-.12	-.11	-.00	-.00	-.01	**-1.29***	**-1.24***	**-1.27***	-.15	-.15	-.19
	7+ members	-.02	-.02	-.02	-.06	-.09	-.07	-.03	-.03	-.03	-.04	-.04	-.04	-.91	-.77	-.90	-.16	-.13	-.16
Child Sex	Female																		
	Male	-.04	-.03	-.04	**.46****	**.45****	**.45****	.09	.07	.09	**.05***	**.05***	**.05***	-.07	-.16	-.07	-.21	-.10	-.21
Child age	9.0 – 10.12																		
	11.0 – 12.12	.01	.01	.01	**.27***	**.24***	**.27***	-.06	-.06	-.06	**.11****	**.11****	**.11****	.56	.64	.59	.77	.91	.75
	13.0 – 15.12	.06	.06	.06	-.01	-.05	-.01	.05	.03	.05	**.13****	**.13****	**.14****	.94	.96	.98	.84	1.00	.84
Maternal Education	≥ Secondary																		
	<=Primary	-.06	-.07	-.06	-.03	-.05	-.05	-.02	-.01	-.03	-.01	-.02	-.02	-.79	-.77	-.79	.24	.12	.21
Maternal Employment	Employed																		
	Unemployed	.02	.01	.02	.11	.10	.12	.06	.05	.06	**-.04***	**-.05***	**-.04***	-.04	.00	-.04	.05	-.01	.08
Maternal (G/C/P) Drinking	No																		
	Yes	-.03	-.02	-.04	-.13	-.09	.06	-.05	-.08	-.03	-.02	-.02	.01	.22	.66	.50	-.43	-.50	.03
Model Fit	F statistic	1.36	1.50	1.41	**3.41****	**3.37****	**3.38****	0.75	0.76	0.73	**3.84****	**3.98****	**3.85****	1.42	1.44	1.46	1.01	1.09	2.36
	R^2	.042	.045	.043	.103	.101	.103	.024	.024	.023	.110	.112	.110	.044	.044	.045	.031	.033	.030
	R^2 Adjusted	.011	.015	.013	.073	.071	.072	-.008	-.008	-.009	.081	.084	.081	.013	.013	.014	.000	.003	-.001
Effect Size	Cohen's f^2	.044	.047	.045	.115	.112	.115	.025	.025	.024	.124	.126	.124	.046	.046	.047	.032	.034	.031

*Note: ***p < .05, **p <0.01**

[a] Note: For each of the models the 'G' suffix indicates maternal gestational drinking, the 'C' suffix indicates current maternal drinking and the 'P' suffix indicates past maternal drinking

[b] Note: *B* = unstandardized beta values. More detailed versions of this table for each subtest with additional statistics, namely: *SE*, *95% CI* and *β* for each *B* are provided in tables C-H in the supplementary materials section

Discussion

Contrary to the findings of previous local research, the results of this study indicate that maternal gestational drinking, current maternal drinking and past maternal drinking were not significantly associated with performance across all of the EF subtests (Adnams et al., 2001; Katwan et al., 2011; Rochat et al., 2019). However, it is notable that for maternal gestational and current drinking behaviours, children of self-reported drinking mothers generally performed non-significantly worse across all EF subtests compared to children of self-reported non-drinking mothers, although this pattern was less clear for past maternal drinking. These non-significant findings are arguably due to the small effect sizes (Cohen's f^2) found across each of the models, 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 EF outcomes more broadly, for which the effects of the maternal alcohol use behaviours examined may be more subtle (Katwan, 2010; Katwan et al., 2011).

In terms of the general, maternal specific and child specific socio-demographic factors, the results of this study are also not entirely consistent with previous research findings. The current study's results indicated that none of the included socio-demographic predictors were consistently significantly associated with performance across all of the EF subtests as was predicted based on previous research (Aran-Filippetti & Richaud de Minzi, 2012; Bernier et al., 2010; Conners et al., 2004; Farah et al., 2006; Gur et al., 2012; C. Hughes & R. Devine, 2019; Hughes & Ensor, 2009; Knopik et al., 2006; Mezzacappa, 2004; Raver et al., 2013; Sarsour et al., 2011). However, in four of the EF subtests (namely the MOT, RTI, MTT and SWM subtests) specific levels of certain socio-demographic variables were found to act as significant predictors of subtest specific EF performance. Moreover, for the two CANTAB subtests (RTI and MTT) whose models were found to be significant overall, the child specific socio-demographic factors of child age and child sex were found to act as significant predictors of performance on each of these subtests. As such, these findings provide at least partial support for several of the predicted associations between the socio-demographic factors and the EF outcomes.

Associations Between Maternal Drinking Behaviours and Child EF

Apart from the small effect size explanation, there are two notable alternative explanations for the non-significant associations that were found between the maternal alcohol consumption behaviours of interest and the child EF outcomes. The first explanation for these non-significant findings, could be due to issues pertaining to the use of self-report measures to collect data regarding maternal alcohol use behaviours. Mothers and proxy respondents in our sample may have been less likely to report maternal alcohol use behaviours due to the social stigma surrounding alcohol use, or may have under-reported due to gendered social norms regarding drinking behaviours amongst women in rural areas of South Africa (Rochat et al., 2019; Van de Mortel, 2008).

A second possible explanation for the non-significant associations found between maternal alcohol use behaviours and child EF outcomes, could be due to confounding or residual confounding. Pesticide exposure could be one such factor, as this exposure has been shown to pose a risk for adverse child neurocognitive outcomes (González-Alzaga et al., 2014; London et al., 2012) and has also been shown to impact on maternal mental health (Motsoeneng & Dalvie, 2015) with poor maternal mental health being associated with higher levels of maternal alcohol use behaviours (Davis, Rotheram-Borus, Weichle, Rezai, & Tomlinson, 2017). Interpersonal violence (IPV) is another factor to consider, as recent research has shown that exposure to marital conflict and IPV can have detrimental impacts on child EF abilities (Gustafsson, Coffman, & Cox, 2015; McCoy & Raver, 2014; Samuelson, Krueger, Burnett, & Wilson, 2010; Samuelson, Krueger, & Wilson, 2012), and has also shown that IPV is related to maternal drinking behaviours (Davis et al., 2017). The current study endeavored to control for pesticide exposure by including a residence predictor, as families living on farms were expected to be more exposed, however this factor may not have adequately controlled for pesticide exposure. Moreover, although current study did include several predictors relating to household stability, not specifically controlling for IPV could have resulted in residual confounding.

While no consistent significant associations between the maternal drinking behaviour predictors and the child EF outcomes were found in the current study, there were several notable patterns of performance differences across the EF tasks between children of self-reported drinking versus self-reported non-drinking mothers. In line with the findings from a previous study (N=68) conducted within the WC, which 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), the current study found that children of mothers who reported drinking during pregnancy performed worse (on average, see Table 2) across the EF subtests as compared to children of mothers who reported that they did not drink during pregnancy (Adnams et al., 2001). Moreover, in support of previous 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). In the current study, mothers who reported past drinking were only seen to perform worse (on average, see Table 2) on three of the six EF subtests. Moreover, the unstandardized beta values (*B*) for children of mothers who reported past drinking were only negative for two out of the six EF subtests, indicating that there was a lack of evidence for a consistent negative association between past maternal drinking and performance across all of the EF subtests.

Associations Between Socio-demographic Factors and Child EF

Contrary to what was predicted based on previous research, none of the socio-demographic predictors included in the models on an a priori basis were found to be consistently significantly associated with performance across all of the assessed EF outcomes. However, the results of the current study show that there were several instances (detailed below) where certain levels of the socio-demographic predictors were found to be significantly associated with specific EF outcomes. These findings provide at least partial support for the predicted impacts of these socio-demographic factors on child EF outcomes, which can be compared and contrasted with previous research.

Notably, out of all the eighteen MR models that were run, only the models for the RTI and MTT subtests were found to be significant overall (see Table 3). For these models, across both subtests, the child specific socio-demographic predictors of child age and child sex were found to act as significant predictors of these subtests' outcomes. Previous research, which has used electronic batteries comparable to the one used in the current study, has shown that child neurocognitive functions, and specifically their EF capacities mature and develop over time

(De Luca et al., 2003; Gur et al., 2012; Roalf et al., 2014). In line with this research, in the current study it was found that children in the older age groups performed significantly better than children from the younger age groups on the RTI and MTT subtests, which assessed processing speed and multi-tasking abilities respectively (De Luca et al., 2003; Gur et al., 2012; Roalf et al., 2014).

Moreover, with regards to gender differences in EF performance, in line with previous research it was found that boys significantly outperformed girls on the RTI, a test of processing speed, and the MTT subtest which required response to orienting cues (Gur et al., 2012; Mezzacappa, 2004). However, contrary to previous research findings by Gur and colleagues (2012) which also used an electronic EF battery, girls were not found to significantly outperform boys on the CANTAB EF subtests which assessed memory, namely the SWM and PAL (Gur et al., 2012).

For both the maternal specific and the general socio-demographic factors there were only three instances where specific socio-demographic factors consistently predicted significant differences in EF performance across all three of the maternal drinking models. The first instance can be found in the MOT processing speed subtest, where in terms of the predictor home language it can be seen that non-Afrikaans speaking children performed significantly worse than Afrikaans speaking children on this subtest. A potential explanation for this finding could be due to the fact that South African public schools generally only provide educational instruction in Afrikaans or English which is arguably disadvantageous to children who speak a different home language (Taylor & von Fintel, 2016).

The second instance of a socio-demographic variable acting as a significant predictor of EF performance across all the maternal alcohol use models is in the MTT subtest, a test of multitasking and attention. Within this subtest it was found that for the maternal employment predictor children of unemployed mothers performed significantly worse than children of employed mothers. These findings are consistent with previous international research, which has shown that maternal unemployment and consequent financial instability have negative consequences for child neurocognitive functioning and development (Bornstein & Bradley, 2014; González et al., 2018).

The last instance of a socio-demographic variable acting as significant predictor of EF performance across all the maternal alcohol use models is in the SWM subtest, a test of memory. Within this subtest it was found that for the household size predictor, children from households with 5-6 members performed significantly worse than children from households with 2-4 members. In support of this finding, local research has indicated that larger households in South Africa are more likely to be poor, with international research indicating strong links between poverty and deficits in child neurocognitive outcomes (Jensen et al., 2017; Sekhampu, 2013).

Strengths and Limitations

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 alcohol consumption behaviours (apart from gestational drinking) on child neurocognitive outcomes. Secondly, this study addresses a gap in the international literature by providing initial evidence for the impacts of several socio-demographics on child neurocognitive outcomes within the context of a LMIC. 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 variations in child EF capabilities, but it has yet to be used to examine said outcomes within the context of South Africa.

However, although this study has several strengths, several limitations have also been identified in the discussion above, including: a potential lack of power to detect the small effect sizes found during modelling, possible residual confounding through pesticide exposure and

IPV, and potential under-reporting of maternal drinking behaviours due to the use of self-report measures which are known to be subject to response bias. Another major limitation of this research relates to its cross-sectional design which means that the temporality of the relations between the exposures (maternal alcohol use behaviours and related socio-demographic factors) and the outcomes (child EFs) of interest cannot be determined.

Conclusions

The findings of the current study provide initial insights into the impacts of different types of maternal drinking behaviours (before, during and after pregnancy) and related socio-demographic factors on developmentally sensitive child neurocognitive outcomes (specifically child EF) within the context of a LMIC, South Africa. In terms of this study's findings, although no significant associations were found between the examined maternal alcohol use behaviours and child EFs, there were several notable patterns of performance differences between children self-reported drinking and children of self-reported non-drinking mothers which require further exploration in research employing larger samples that are more adequately powered. Moreover, several socio-demographic factors, including: home language, child age, child sex, maternal employment and household size, were found to act as significant predictors (p <.05) of subtest specific child EF performance. This finding provides initial evidence for the impacts of these specific socio-demographic factors on child EF outcomes within the context of a developing country (South Africa), a finding which requires corroboration through further research in similar settings using comparable research methods.

References

Adnams, C. M., Kodituwakku, P. W., Hay, A., Molteno, C. D., Viljoen, D., & May, P. A. (2001). Patterns of cognitive-motor development in children with fetal alcohol syndrome from a community in South Africa. *Alcoholism: Clinical and Experimental Research, 25*(4), 557-562.

Aran-Filippetti, V., & Richaud de Minzi, M. C. (2012). A structural analysis of executive functions and socioeconomic status in school-age children: Cognitive factors as effect mediators. *The Journal of Genetic Psychology, 173*(4), 393-416.

Ardila, A., Rosselli, M., Matute, E., & Guajardo, S. (2005). The influence of the parents' educational level on the development of executive functions. *Developmental neuropsychology, 28*(1), 539-560.

Bernier, A., Carlson, S. M., & Whipple, N. (2010). From external regulation to self-regulation: Early parenting precursors of young children's executive functioning. *Child development, 81*(1), 326-339.

Bornstein, M. H., & Bradley, R. H. (2014). *Socioeconomic status, parenting, and child development*: Routledge.

Brocki, K. C., & Bohlin, G. (2004). Executive functions in children aged 6 to 13: A dimensional and developmental study. *Developmental neuropsychology, 26*(2), 571-593.

Chen, H., Cohen, P., & Chen, S. (2010). How big is a big odds ratio? Interpreting the magnitudes of odds ratios in epidemiological studies. *Communications in Statistics—simulation and Computation®, 39*(4), 860-864.

Chetty-Mhlanga, S., Basera, W., Fuhrimann, S., Probst-Hensch, N., Delport, S., Mugari, M., . . . Dalvie, M. A. (2018). 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, 18*(1), 857.

Conners, N. A., Bradley, R. H., Mansell, L. W., Liu, J. Y., Roberts, T. J., Burgdorf, K., & Herrell, J. M. (2004). Children of mothers with serious substance abuse problems: An accumulation of risks. *Am J Drug Alcohol Abuse, 30*(1), 85-100. doi:10.1081/ada-120029867

Croxford, J., & Viljoen, D. (1999). Alcohol consumption by pregnant women in the Western Cape. *South African Medical Journal, 89*(9).

Davis, E. C., Rotheram-Borus, M. J., Weichle, T. W., Rezai, R., & Tomlinson, M. (2017). Patterns of alcohol abuse, depression, and intimate partner violence among township mothers in South Africa over 5 years. *AIDS and Behavior, 21*(2), 174-182.

De Luca, C. R., Wood, S. J., Anderson, V., Buchanan, J.-A., Proffitt, T. M., Mahony, K., & Pantelis, C. (2003). Normative data from the CANTAB. I: Development of executive function over the lifespan. *Journal of clinical and experimental neuropsychology, 25*(2), 242-254.

Ellis, S., & Steyn, H. (2003). Practical significance (effect sizes) versus or in combination with statistical significance (p-values): Research note. *Management dynamics: journal of the southern african institute for management scientists, 12*(4), 51-53.

Farah, M. J., Shera, D. M., Savage, J. H., Betancourt, L., Giannetta, J. M., Brodsky, N. L., . . . Hurt, H. (2006). Childhood poverty: Specific associations with neurocognitive development. *Brain Res, 1110*(1), 166-174. doi:10.1016/j.brainres.2006.06.072

Ferguson, K. T., Cassells, R. C., MacAllister, J. W., & Evans, G. W. (2013). The physical environment and child development: An international review. *Int J Psychol, 48*(4), 437-468. doi:10.1080/00207594.2013.804190

Goldberg, M. C., Mostofsky, S. H., Cutting, L. E., Mahone, E. M., Astor, B., Denckla, M. B., & Landa, R. (2005). Subtle executive impairment in children with autism and children with ADHD. *Journal of autism and developmental disorders, 35*(3), 279-293.

González, L., Cortés-Sancho, R., Murcia, M., Ballester, F., Rebagliato, M., & Rodríguez-Bernal, C. L. (2018). The role of parental social class, education and unemployment on child cognitive development. *Gaceta sanitaria*.

González-Alzaga, B., Lacasaña, M., Aguilar-Garduño, C., Rodríguez-Barranco, M., Ballester, F., Rebagliato, M., & Hernández, A. (2014). A systematic review of neurodevelopmental effects of prenatal and postnatal organophosphate pesticide exposure. *Toxicology letters, 230*(2), 104-121.

Green, C., Mihic, A., Nikkel, S., Stade, B., Rasmussen, C., Munoz, D., & Reynolds, J. (2009). Executive function deficits in children with fetal alcohol spectrum disorders (FASD) measured using the Cambridge Neuropsychological Tests Automated Battery (CANTAB). *Journal of Child Psychology and Psychiatry, 50*(6), 688-697.

Gur, R. C., Richard, J., Calkins, M. E., Chiavacci, R., Hansen, J. A., Bilker, W. B., . . . Mentch, F. D. (2012). Age group and sex differences in performance on a computerized neurocognitive battery in children age 8− 21. *Neuropsychology, 26*(2), 251.

Gustafsson, H. C., Coffman, J. L., & Cox, M. J. (2015). Intimate partner violence, maternal sensitive parenting behaviors, and children’s executive functioning. *Psychology of violence, 5*(3), 266.

Hughes, C., & Devine, R. (2019). For Better or for Worse? Positive and Negative Parental Influences on Young Children's Executive Function. *Child development, 90*(2), 593-609.

Hughes, C., & Ensor, R. (2009). How do families help or hinder the emergence of early executive function? *New Dir Child Adolesc Dev, 2009*(123), 35-50. doi:10.1002/cd.234

Jensen, S. K., Berens, A. E., & Nelson 3rd, C. A. (2017). Effects of poverty on interacting biological systems underlying child development. *The Lancet Child & Adolescent Health, 1*(3), 225-239.

Katwan, E. (2010). *Case-contol study of the association of use of health services by children with behavioural and developmental disorders with prenatal alcohol exposure.* (Masters of Public Health). University of Cape Town, Cape Town.

Katwan, E., Adnams, C., & London, L. (2011). Childhood behavioural and developmental disorders. *SAMJ: South African Medical Journal, 101*(10), 724-727.

Knopik, V. S., Heath, A. C., Jacob, T., Slutske, W. S., Bucholz, K. K., Madden, P. A., . . . Martin, N. G. (2006). Maternal alcohol use disorder and offspring ADHD: Disentangling genetic and environmental effects using a children-of-twins design. *Psychological medicine, 36*(10), 1461-1471.

London, L. (1999). Thedop'system, alcohol abuse and social control amongst farm workers in South Africa: A public health challenge. *Social Science & Medicine, 48*(10), 1407-1414.

London, L., Beseler, C., Bouchard, M. F., Bellinger, D. C., Colosio, C., Grandjean, P., . . . Stallones, L. (2012). Neurobehavioral and neurodevelopmental effects of pesticide exposures. *Neurotoxicology, 33*(4), 887-896. doi:10.1016/j.neuro.2012.01.004

Luciana, M., & Nelson, C. A. (2002). Assessment of neuropsychological function through use of the Cambridge Neuropsychological Testing Automated Battery: Performance in 4-to 12-year-old children. *Developmental neuropsychology, 22*(3), 595-624.

Mattson, S. N., Roesch, S. C., Fagerlund, Å., Autti-Rämö, I., Jones, K. L., May, P. A., . . . CIFASD. (2010). Toward a neurobehavioral profile of fetal alcohol spectrum disorders. *Alcoholism: Clinical and Experimental Research, 34*(9), 1640-1650.

May, P. A., Brooke, L., Gossage, J. P., Croxford, J., Adnams, C., Jones, K. L., . . . Viljoen, D. (2000). Epidemiology of fetal alcohol syndrome in a South African community in the Western Cape Province. *American journal of public health, 90*(12), 1905.

May, P. A., de Vries, M. M., Marais, A. S., Kalberg, W. O., Adnams, C. M., Hasken, J. M., . . . Hoyme, H. E. (2016). The continuum of fetal alcohol spectrum disorders in four rural communities in South Africa: Prevalence and characteristics. *Drug Alcohol Depend, 159*, 207-218. doi:10.1016/j.drugalcdep.2015.12.023

May, P. A., Gossage, J. P., Brooke, L. E., Snell, C. L., Marais, A.-S., Hendricks, L. S., . . . Viljoen, D. L. (2005). Maternal risk factors for fetal alcohol syndrome in the Western cape province of South Africa: A population-based study. *American journal of public health, 95*(7), 1190-1199.

May, P. A., Gossage, J. P., Marais, A. S., Adnams, C. M., Hoyme, H. E., Jones, K. L., . . . Viljoen, D. L. (2007). The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. *Drug Alcohol Depend, 88*(2-3), 259-271. doi:10.1016/j.drugalcdep.2006.11.007

May, P. A., Gossage, J. P., Marais, A. S., Hendricks, L. S., Snell, C. L., Tabachnick, B. G., . . . Viljoen, D. L. (2008). Maternal risk factors for fetal alcohol syndrome and partial fetal alcohol syndrome in South Africa: A third study. *Alcohol Clin Exp Res, 32*(5), 738-753. doi:10.1111/j.1530-0277.2008.00634.x

McCoy, D. C., & Raver, C. C. (2014). Household instability and self-regulation among poor children. *Journal of Children and Poverty, 20*(2), 131-152.

McKinstry, J. (2005). Using the past to step forward: fetal alcohol syndrome in the Western Cape Province of South Africa. In: American Public Health Association.

Mezzacappa, E. (2004). Alerting, orienting, and executive attention: Developmental properties and sociodemographic correlates in an epidemiological sample of young, urban children. *Child development, 75*(5), 1373-1386.

Motsoeneng, P., & Dalvie, M. (2015). Relationship between urinary pesticide residue levels and neurotoxic symptoms among women on farms in the Western Cape, South Africa. *International Journal of Environmental Research and Public Health, 12*(6), 6281-6299.

Raver, C. C., Blair, C., & Willoughby, M. (2013). Poverty as a predictor of 4-year-olds' executive function: New perspectives on models of differential susceptibility. *Dev Psychol, 49*(2), 292-304. doi:10.1037/a0028343

Rhoades, B. L., Greenberg, M. T., Lanza, S. T., & Blair, C. (2011). Demographic and familial predictors of early executive function development: Contribution of a person-centered perspective. *Journal of Experimental Child Psychology, 108*(3), 638-662.

Roalf, D. R., Gur, R. E., Ruparel, K., Calkins, M. E., Satterthwaite, T. D., Bilker, W. B., . . . Gur, R. C. (2014). Within-individual variability in neurocognitive performance: Age- and sex-related differences in children and youths from ages 8 to 21. *Neuropsychology, 28*(4), 506.

Rochat, T. J., Houle, B., Stein, A., Mitchell, J., & Bland, R. M. (2019). Maternal alcohol use and children's emotional and cognitive outcomes in rural South Africa. *Samj South African Medical Journal, 109*(7), 526-534. doi:10.7196/SAMJ.2019.v109i6.13120

Roque, D. T., Teixeira, R. A. A., Zachi, E. C., & Ventura, D. F. (2011). The use of the Cambridge Neuropsychological Test Automated Battery (CANTAB) in neuropsychological assessment: Application in Brazilian research with control children and adults with neurological disorders. *Psychology & Neuroscience, 4*(2), 255-265.

Samuelson, K. W., Krueger, C. E., Burnett, C., & Wilson, C. K. (2010). Neuropsychological functioning in children with posttraumatic stress disorder. *Child Neuropsychology, 16*(2), 119-133.

Samuelson, K. W., Krueger, C. E., & Wilson, C. (2012). Relationships between maternal emotion regulation, parenting, and children's executive functioning in families exposed to intimate partner violence. *Journal of Interpersonal Violence, 27*(17), 3532-3550.

Sarsour, K., Sheridan, M., Jutte, D., Nuru-Jeter, A., Hinshaw, S., & Boyce, W. T. (2011). Family socioeconomic status and child executive functions: The roles of language, home environment, and single parenthood. *Journal of the International Neuropsychological Society, 17*(1), 120-132.

Sekhampu, T. J. (2013). Determinants of poverty in a South African township. *Journal of Social Sciences, 34*(2), 145-153.

StataCorp. (2015). College Station, TX: 2015. *Stata Statistical Software: Release, 14*.

Taylor, S., & von Fintel, M. (2016). Estimating the impact of language of instruction in South African primary schools: A fixed effects approach. *Economics of Education Review, 50*, 75-89.

Van de Mortel, T. F. (2008). Faking it: Social desirability response bias in self-report research. *Australian Journal of Advanced Nursing, The, 25*(4), 40.

Viljoen, D., Croxford, J., Gossage, J. P., Kodituwakku, P. W., & May, P. A. (2002). Characteristics of mothers of children with fetal alcohol syndrome in the Western Cape Province of South Africa: a case control study. *Journal of Studies on Alcohol, 63*(1), 6-17.

Walker, S. P., Wachs, T. D., Gardner, J. M., Lozoff, B., Wasserman, G. A., Pollitt, E., . . . Group, I. C. D. S. (2007). Child development: Risk factors for adverse outcomes in developing countries. *The lancet, 369*(9556), 145-157.

Walker, S. P., Wachs, T. D., Grantham-McGregor, S., Black, M. M., Nelson, C. A., Huffman, S. L., . . . Lozoff, B. (2011). Inequality in early childhood: Risk and protective factors for early child development. *The lancet, 378*(9799), 1325-1338.

Supplementary Materials

Table A. CANTAB Subtest Outcome Measure Descriptions

EF Domain	EF Subtest	Aspects of EFs Assessed	Description of selected key outcome measure	Statistical Transformation (final subtest outcome measure)
Processing Speed	**MOT**	Attentional allocation/control, motor control	**MOTML:** The mean latency from the display of a stimulus to a correct response to that stimulus during assessment trails, in milliseconds.	This variable was converted to the inverse form to give 'speed' (tasks/ millisecond) then outliers of 3 SDs were removed. Lastly this outcome was converted seconds by / 1000 to give final measure of tasks/second (t/s).
	RTI	Working memory, attentional allocation/control, motor control	**RTIFMDMT:** The median time taken for a subject to release the response button and select the target stimulus after it flashed yellow on screen. Calculated across correct, assessed trials in which the stimulus could appear in any one of five locations. Measured in milliseconds.	This variable was converted to the inverse form to give 'speed' (tasks/ millisecond) then outliers of 3 SDs were removed. Lastly this outcome was converted seconds by / 1000 to give final measure of tasks/second (t/s).[a]
Attention	**RVP**	Sustained attention, attentional control, inhibition (suppressing incorrect response)	**RVPMDL:** The median response latency on trials where the subject responded correctly. Calculated across all assessed trials. Measured in milliseconds.	This variable was converted to the inverse form to give 'speed' (tasks/ millisecond) then outliers of 3 SDs were removed. Lastly this outcome was converted seconds by / 1000 to give final measure of tasks/second (t/s).
	MTT	Cognitive flexibility, set-shifting, task-switching, working memory, attentional control/allocation, inhibition (suppressing incorrect response)	**MTTLMD:** The median latency of response (from stimulus appearance to button press). Calculated across all correct, assessed trials. Measured in milliseconds.	This variable was converted to the inverse form to give 'speed' (tasks/ millisecond) then outliers of 3 SDs were removed. Lastly this outcome was converted seconds by / 1000 to give final measure of tasks/second (t/s).
Memory	**SWM**	Working memory, short term memory, planning, strategy employment, organized search	**SWMBE:** The number of times the subject incorrectly revisits a box in which a token has previously been found. Calculated across all assessed four, six and eight token trials.	This variable was approximately normally distributed (ND) so no transformations were applied, however outliers (3 SDs) were removed for consistency. As this variable measures correct selections (hits) no reversal of this variable is necessary.
	PAL	Short term memory, working memory, planning, strategy employment, attentional allocation	**PALFAMS:** The number of times a subject chose the correct box on their first attempt when recalling the pattern locations. Calculated across all assessed trials.	This variable was approximately normally distributed (ND), however because this variable measures / assesses misses (inaccuracy) instead of hits (accuracy) it was reversed so that a higher score could be interpreted as a better performance, in line with the other outcome measures[b]

Adapted from Chetty-Mhlanga et al., 2018 and the CANTAB the user guide

[a]Note that outcomes measured in milliseconds were inversed and then divided by 1000 to give speed measures in tasks/second (t/s)

[b]Note that this outcome measuring inaccuracy was reversed to give accuracy, measured in 'hits'

Note: For all outcome measures a higher score means a 'better ' (faster or more accurate) performance on the relevant subtest

Table B. Exposure Variables (Predictors)

Type	Predictor Name	Original Format	Questions (Guardian Questionnaire)	Response Choices (Guardian Questionnaire)	Current study coding (used in statistical analyses)
Potential confounders	Study Area	Categorical	Study area:	1. Grabouw 2. Piketberg 3. Hex River Valley	0. Hex River 1. Piketberg 2. Grabouw
	Residence (Farm residence?)	Binary	Is the household located on the property of a farm?	1. Yes 2. No	0. Non-Farm 1. Farm
Maternal alcohol consumption predictors*	Maternal gestational alcohol consumption	Categorical	Did you (/the mother) drink alcohol during pregnancy? *(HINT: If the biological mother is NOT answering the questions, please phrase them accordingly.)*	1. Never 2. Less than 1 glass a day 3. About 1 glass a day 4. More than 1 glass per day	0. No 1. Yes
	Current maternal alcohol consumption	Categorical	Do you (/does the mother) currently drink alcohol? *(HINT: If the biological mother is NOT answering the questions, please phrase them accordingly.)*	1. Never 2. Less than 1 glass a day 3. About 1 glass a day 4. More than 1 glass per day	0. No 1. Yes
	Past maternal alcohol consumption	Categorical	Have you (/has the mother) ever drank alcohol in the past? *(HINT: If the biological mother is NOT answering the questions, please phrase them accordingly.)*	1. Never 2. Less than 1 glass a day 3. About 1 glass a day 4. More than 1 glass per day	0. No 1. Yes
Maternal-specific socio-demographic predictors	Maternal employment	Categorical	Has this **child's** mother/ female guardian been employed in the last 12 months?	1. Yes 2. No	0. Employed 1. Unemployed
	Maternal education level	Categorical	What is the highest level of education completed by the child's mother/female guardian?	0. No schooling 1. Primary education 2. Secondary education 3. Tertiary education	0. ≥ Secondary Education 1. ≤ Primary Education
Child-specific socio-demographic predictors	Child sex	Binary	What is the sex of the child?	0. Male 1. Female	0. Female 1. Male
	Child age	Continuous	What is the child's Date of Birth (DoB)?	Months (DoB till CANTAB test date)	0. 9.00 – 10.12 yrs.mnths 1. 11.00 – 12.12 yrs.mnths 2. 13.00 – 15.12 yrs.mnths
General socio-demographic predictors (relating to SES)	Household size	Discrete	How many people live in this household?	Number of members living in same household as the child participant	0. 2-4 members 1. 5-5 members 2. 7+ members
	Parental marital status	Categorical	What is the child's mother and father's marital status?	1. Married/Cohabiting 2. Widowed 3. Divorced/Separated 4. Never married / Never lived together	0. Married 1. Never Married 2. Other (divorced/ separated / widowed)
	Home Language	Categorical	What is your first / home language?	1. Afrikaans 2. IsiXhosa 3. English 4. IsiZulu 5. SeSotho 6. IsiNdebele 7. SiSwati 8. Xitsonga 9. Sepedi 10. Tshivenda 11. Setswana 12. Other	0. Afrikaans 1. Non-Afrikaans

*Note: the maternal alcohol consumption predictors were collapsed into binary format, with the 'Never' level being recoded as 'No' meaning no alcohol usage, and the other categories (<1, ≈1, >1 glass/day) being collapsed into 'Yes'

Table C. The MR relationships between the predictors and the MOTML processing speed outcome [tasks per second (t/s)]

SUBTEST	MOT (tasks/sec)	**Model 1: Maternal Gestational Drinking N=450**				**Model 2: Maternal Current Drinking N=456**				**Model 3: Maternal Past Drinking N=450**			
Categorical variable	Category Coefficients	*B*	*SE*	*95% CI*	*β*	*B*	*SE*	*95 % CI*	*β*	*B*	*SE*	*95% CI*	*β*
Constant	Intercept	**1.28****	.07	1.14, 1.41	.	**1.28****	.07	1.15, 1.41	.	**1.29****	.07	1.16, 1.42	.
Area	De Doorns												
	Piketberg	**-.13***	.06	-.25, -.01	-.15	**-.12***	.06	-.24, -.00	-.14	**-.13***	.06	-.25, -.01	-.15
	Grabouw	-.02	.06	-.14, .10	-.02	-.01	.06	-.13, .12	-.01	-.01	.06	-.13, .11	-.01
Residence	Non-Farm												
	Farm	.01	.05	-.09, .10	.01	.01	.05	-.08, .10	.01	.01	.05	-.09, .10	.01
Home Language	Afrikaans												
	Non-Afrikaans	**-.12***	.06	-.23, -.01	-.14	**-.13***	.06	-.24, -.02	-.15	**-.12***	.06	-.23, -.01	-.14
Parental Marital Status	Married												
	Never Married	-.08	.04	-.16, .00	-.10	-.08	.04	-.16 , .01	-.10	**-.09***	.04	-.17, -.01	-.11
	Other	-.06	.05	-.17, .05	-.06	-.07	.05	-.17, .04	-.07	-.06	.05	-.17, .04	-.06
Household Size	2-4 Members												
	5-6 Members	.01	.04	-.08, .09	.01	.01	.04	-.08, .09	.01	.01	.04	-.08, .09	.01
	7+ members	-.02	.05	-.11, .08	-.02	-.02	.05	-.12, .08	-.02	-.02	.05	-.12, .08	-.02
Child Sex	Female												
	Male	-.04	.04	-.11, .04	-.05	-.03	.04	-.10, .04	-.04	-.04	.04	-.11, .04	-.05
Child age	9.0 – 10.12												
	11.0 – 12.12	.01	.04	-.08, .10	.01	.01	.04	-.08, .10	.01	.01	.04	-.08, .09	.01
	13.0 – 15.12	.06	.05	-.04, .16	.07	.06	.05	-.03, .16	.07	.06	.05	-.04, .15	.06
Maternal Education	≥ Secondary												
	<=Primary	-.06	.04	-.14, .02	-.08	-.07	.04	-.15, .00	-.09	-.06	.04	-.14, .01	-.08
Maternal Employment	Employed												
	Unemployed	.02	.04	-.07, .10	.02	.01	.05	-.07, .09	.01	.02	.04	-.07, .10	.02
Maternal (G/C/P) Drinking	No												
	Yes	-.03	.06	-.16, .09	-.03	-.02	.04	-.11, .06	-0.03	-.04	.04	-.12, .05	-.04
Model Fit	F statistic	F(14, 435) =1.36, Prob > F = .170				F(14, 441) =1.50, Prob> F = .107				F(14, 435) =1.41, Prob>F = 0.146			
	R^2	R^2 = .042				R^2 = .045				R^2 = .043			
	R^2 Adjusted	Adjusted R^2 = .011				Adjusted R^2 = 0.015				Adjusted R^2 = .013			
Effect Size[a]	Cohen's f^2	f^2 = .044				f^2 = .047				f^2 = .045			

$^{*}p < .05$, $^{**}p < 0.01$

[a]Note: Cohen's $f^2 = R^2 / 1 – R^2$

Table D. The MR relationships between the predictors and the RTIFMDMT processing speed outcome [tasks per second (t/s)]

SUBTEST	RTI (tasks/sec)	**Model 4: Maternal Gestational Drinking N=429**				**Model 5: Maternal Current Drinking N=433**				**Model 6: Maternal Past Drinking N=428**			
Categorical variable	Category Coefficients	*B*	*SE*	*95% CI*	*β*	*B*	*SE*	*95 % CI*	*β*	*B*	*SE*	*95% CI*	*β*
Constant	Intercept	**3.98****	.17	3.64, 4.31	.	**3.99****	.16	3.65, 4.33	.	**3.96****	.17	3.62, 4.30	.
Area	De Doorns												
	Piketberg	.14	.16	-.16, .44	.06	.15	.16	-.16, .46	.07	.14	.16	-.17, .44	..06
	Grabouw	.29	.16	-.02, .60	.12	.32	.16	.01, .63	.13	.28	.16	-.03, .60	.12
Residence	Non-Farm												
	Farm	-.16	.12	-.40, .08	-.07	-.14	.12	-.37, .10	-.06	-.15	.12	-.39, .08	-.07
Home Language	Afrikaans												
	Non-Afrikaans	-.09	.15	-.38, .19	-.04	-.09	.15	-.38, .19	-.04	-.08	.15	-.36, .21	-.04
Parental Marital Status	Married												
	Never Married	.13	.11	-.09, .34	.06	.15	.11	-.07, .36	.07	.12	.11	-.09, .34	.06
	Other	.23	.14	-.04, .50	.09	.26	.14	-.01, .53	.10	.22	.14	-.05, .49	.09
Household Size	2-4 Members												
	5-6 Members	-.02	.11	-.23, .20	-.01	-.01	.11	-.22, .21	-.00	-.03	.11	-.25, .19	-.01
	7+ members	-.06	.13	-.32, .19	-.03	-.09	.13	-.34, .17	-.04	-.07	.13	-.32, .19	-.03
Child Sex	Female												
	Male	**.46****	.10	.27, .64	.23	**.45****	.10	.27, .64	.22	**.45****	.10	.27, .64	.23
Child age	9.0 – 10.12												
	11.0 – 12.12	**.27***	.11	.05, .49	.13	**.24***	.11	.02, .46	.11	**.27***	.11	.05, .49	.13
	13.0 – 15.12	-.01	.13	-.26, .24	-.00	-.05	.13	-.30, .21	-.02	-.01	.13	-.26, .24	-.00
Maternal Education	≥ Secondary												
	<=Primary	-.03	.10	-.23, .17	-.02	-.05	.10	-.25, .15	-.03	-.05	.10	-.24, .15	-.02
Maternal Employment	Employed												
	Unemployed	.11	.11	-.09, .32	.05	.10	.11	-.11, .30	.05	.12	.11	-.09, .33	.06
Maternal (G/C/P) Drinking	No								-				
	Yes	-.13	.16	-.46 , .19	-.04	-.09	.11	-.31, .13	-.04	.06	.11	-.16, .27	.03
Model Fit	F statistic	F(14, 414) = 3.41, Prob > F = **.000****				F(14, 418) = 3.37, P > F = **.000****				F(14, 413) = 3.38, Prob > F = **.000****			
	R^2	R^2 = .103				R^2 = .101				R^2 = .103			
	R^2 Adjusted	Adjusted R^2 = .073				Adjusted R^2 = .071				Adjusted R^2 = .072			
Effect size	Cohen's f^2	f^2 = .115				f^2 = .112				f^2 = .115			

$^{*}p < .05$, $^{**}p < 0.01$

Table E. The MR relationships between the predictors and the RVPMDL attention outcome [tasks per second (t/s)]

SUBTEST	**RVP (tasks/sec)**	**Model 7: Maternal Gestational Drinking N=441**				**Model 8: Maternal Current Drinking N=447**				**Model 9: Maternal Past Drinking N=441**			
Categorical variable	Category Coefficients	*B*	*SE*	*95% CI*	*β*	*B*	*SE*	*95 % CI*	*β*	*B*	*SE*	*95% CI*	*β*
Constant	Intercept	**2.36****	.12	2.13, 2.60	.	**2.37****	.12	2.14, 2.61	.	**2.36****	.12	2.12, 2.60	.
Area	De Doorns												
	Piketberg	.01	.11	-.20, .23	.01	.05	.11	-.17, .27	.03	.02	.11	-.20, .24	.01
	Grabouw	.05	.11	-.17, ,27	.03	.07	.07	-.16, .30	.04	.05	.12	-.18, .28	.03
Residence	Non-Farm												
	Farm	-.00	.09	-.17, .17	-.00	-.00	.09	-.17, .17	-.00	.01	.09	-.16, .18	.01
Home Language	Afrikaans												
	Non-Afrikaans	.14	.10	-.07, .34	.10	.14	.10	-.06, .35	.10	.14	.10	-.06, .35	.10
Parental Marital Status	Married												
	Never Married	.01	.08	-.14, .16	.01	.03	.08	-.12, .18	.02	.01	.08	-.15, .16	.01
	Other	.04	.10	-.15, .23	.02	.05	.10	-.14, .24	.03	.04	.10	-.15, .23	.02
Household Size	2-4 Members												
	5-6 Members	-.11	.08	-.27, .04	-.08	-.12	.08	-.27, .04	-.08	-.11	.08	-.27, .04	-.08
	7+ members	-.03	.09	-.21, .15	-.02	-.03	.09	-.21, .16	-.02	-.03	.09	-.21, .16	-.02
Child Sex	Female												
	Male	.09	.07	-.04, .22	.06	.07	.07	-.06, .21	.05	.09	.07	-.05, .22	.06
Child age	9.0 – 10.12												
	11.0 – 12.12	-.06	.08	-.22, .10	-.04	-.06	.08	-.22, .09	-.04	-.06	.08	-.22, .09	-.04
	13.0 – 15.12	.05	.09	-.12, .23	.03	.03	.09	-.14, .21	.02	.05	.09	-.12, .23	.03
Maternal Education	≥ Secondary												
	<=Primary	-.02	.07	-.16, .12	-.02	-.01	.07	-.15, .12	-.01	-.03	.07	-.17, .12	-.02
Maternal Employment	Employed												
	Unemployed	.06	.07	-.08, .21	.05	.05	.07	-.10, .19	.03	.06	.07	-.08, .21	.04
Maternal (G/C/P) Drinking	No												
	Yes	-.05	.11	-.27, .17	-.02	-.08	.08	-.24, .07	.05	-.03	.08	-.19, .12	-.02
Model Fit	F statistic	$F(14, 426) = 0.75$, Prob > F = .721				$F(14, 432) = 0.76$, Prob> F = .718				$F(14, 426) = 0.73$, Prob>F = 0.745			
	R^2	$R^2 = .024$				$R^2 = .024$				$R^2 = .023$			
	R^2 Adjusted	Adjusted $R^2 = -.008$				Adjusted $R^2 = -.008$				Adjusted $R^2 = -.009$			
Effect size	Cohen's f^2	$f^2 = .025$				$f^2 = .025$				$f^2 = .024$			

$^{*}p < .05$, $^{**}p < 0.01$

Table F. The MR relationships between the predictors and the MTTLMD attention outcome [tasks per second (t/s)]

SUBTEST	**MTT (tasks/sec)**	**Model 10: Maternal Gestational Drinking N=451**				**Model 11: Maternal Current Drinking N=456**				**Model 12: Maternal Past Drinking N=451**			
Categorical variable	Category Coefficients	*B*	*SE*	*95% CI*	*β*	*B*	*SE*	*95 % CI*	*β*	*B*	*SE*	*95% CI*	*β*
Constant	Intercept	**1.23****	.04	1.16, 1.30	.	**1.23****	.04	1.16, 1.30	.	**1.23****	.04	1.16, 1.30	.
Area	De Doorns												
	Piketberg	.02	.03	-.04, .09	.05	.03	.03	-.04, .09	.06	.02	.03	-.04, .09	.05
	Grabouw	.04	.03	-.03, .10	.07	.04	.03	-.02, .11	.09	.04	.03	-.03, .10	.07
Residence	Non-Farm												
	Farm	.03	.03	-.02, .08	.05	.03	.02	-.02, .07	.05	.03	.03	-.02, .08	.06
Home Language	Afrikaans												
	Non-Afrikaans	-.01	.03	-.07, .05	-.03	-.01	.03	-.07, .05	-.03	-.01	.03	-.07, .05	-.02
Parental Marital Status	Married												
	Never Married	.02	.02	-.02, .07	.05	.03	.02	-.02, .07	.06	.02	.02	-.02, .07	.05
	Other	.02	.03	-.03, .08	.04	.03	.03	-.03, .08	.05	.02	.03	-..03, .08	.04
Household Size	2-4 Members												
	5-6 Members	-.00	.02	-.05, .04	.05	-.00	.02	-.05, .04	-.01	-.01	-.01	-.05, .04	-.01
	7+ members	-.04	.03	-.09, .02	.04	-.04	.03	-.09, .01	-.08	-.04	-.04	-.09, .01	-.08
Child Sex	Female												
	Male	**.05***	.02	.01, .08	.11	**.05***	.02	.01, 09	.11	.05*	.05	.01, .08	.11
Child age	9.0 – 10.12												
	11.0 – 12.12	**.11****	.02	.06, .15	.24	**.11****	.02	.06, .15	.24	**.11****	.11	.06, .15	.23
	13.0 – 15.12	**.13****	.03	.08, .19	.27	**.13****	.03	.08, .18	.27	**.14****	.14	.08, .19	.28
Maternal Education	≥ Secondary												
	<=Primary	-.01	.02	-.06, .03	.03	-.02	.02	-.06, .02	-.04	-.02	.02	-.06, .03	-.04
Maternal Employment	Employed												
	Unemployed	**-.04***	.02	-.08, .00	-.09	**-.05***	.02	-.09, -.00	-.10	**-.04***	.02	-.08, .00	-.09
Maternal (G/C/P) Drinking	No												
	Yes	-.02	.03	-.08, .05	-.02	-.02	.02	-.07, .02	-.04	.01	.01	-.04, .05	.01
Model Fit:	F statistic	$F(14, 436) = 3.84$ Prob > F = **.000****				$F(14, 441) = 3.98$ Prob> F = **.000****				$F(14, 436) = 3.85$, Prob>F = **.000****			
	R^2	$R^2 = .110$				$R^2 = .112$				$R^2 = .110$			
	R^2 Adjusted	Adjusted $R^2 = .081$				Adjusted $R^2 = .084$				Adjusted $R^2 = .081$			
Effect size	Cohen's f^2	$f^2 = .124$				$f^2 = .126$				$f^2 = .124$			

$^{*}p < .05$, $^{**}p < 0.01$

Table G. The MR relationships between the predictors and the SWMBE memory outcome [accuracy i.e. number of hits]

SUBTEST	SWM (hits)	Model 13: Maternal Gestational Drinking N=451				Model 14: Maternal Current Drinking N=457				Model 15: Maternal Past Drinking N=451			
Categorical variable	Category Coefficients	*B*	*SE*	*95% CI*	*β*	*B*	*SE*	*95 % CI*	*β*	*B*	*SE*	*95% CI*	*β*
Constant	Intercept	**14.61****	.93	12.78, 16.44	.	**14.47****	.93	12.65, 16.29	.	**14.48****	.94	12.63, 16.32	..
Area	De Doorns												
	Piketberg	-1.22	.85	-2.89, .44	-.10	-1.33	.85	-3.00, .34	-.11	-1.28	.85	-2.94, .39	-.11
	Grabouw	-.51	.86	-2.20, 1.18	-.04	-.69	.86	-2.39, 1.01	-.05	-.60	.86	-2.29, 1.10	-.05
Residence	Non-Farm												
	Farm	.56	.66	-.74, 1.86	.05	.55	.66	-.74, 1.83	.05	.56	.66	-.74, 1.85	.05
Home Language	Afrikaans												
	Non-Afrikaans	.02	.80	-1.55, 1.59	.00	.04	.79	-1.52, 1.59	.00	.04	.79	-1.52, 1.60	.00
Parental Marital Status	Married												
	Never Married	.45	.59	-.70, 1.60	.04	.39	.58	-.76, 1.53	.04	.50	.58	-.65, 1.65	.05
	Other	.07	.76	-1.41, 1.56	.01	.02	.75	-1.44, 1.49	.00	.09	.75	-1.39, 1.57	.01
Household Size	2-4 Members												
	5-6 Members	**-1.29***	.60	-2.47. -.11	-.12	**-1.24***	.59	-2.40, -.09	-.11	**-1.27***	.59	-2.44, -.11	-.11
	7+ members	-.91	.70	-2.29, .48	-.07	-.77	.70	-2.14, .60	-.06	-.90	.70	-2.28, .48	-.07
Child Sex	Female												
	Male	-.07	.51	-1.08, .94	-.01	-.16	.51	-1.16, .85	-.01	-.07	.51	-1.08, .94	-.01
Child age	9.0 – 10.12												
	11.0 – 12.12	.56	.61	-.64, 1.76	.05	.64	.60	-.54, 1.81	.06	.59	.61	-.60, 1.79	.05
	13.0 – 15.12	.94	.68	-.40, 2.28	.08	.96	.68	-.37, 2.29	.08	.98	.69	-.37, 2.32	.08
Maternal Education	≥ Secondary												
	<=Primary	-.79	.55	-1.86, .29	-.07	-.77	.54	-1.83, .29	-.07	-.79	.54	-1.86, .28	-.07
Maternal Employment	Employed												
	Unemployed	-.04	.57	-1.16, 1.08	-.00	.00	.56	-1.11, 1.11	.00	-.04	.57	-1.15, 1.08	-.00
Maternal (G/C/P) Drinking	No												
	Yes	.22	.87	-1.49, 1.94	.01	.66	.59	-.50, 1.82	.06	.50	.60	-.67, 1.67	.04
Model Fit	F statistic	F(14, 436) =1.42, Prob > F = .141				F(14, 442) =1.44, Prob> F = .131				F(14, 436) =1.46, Prob>F = 0.121			
	R^2	R^2 = .044				R^2 = .044				R^2 = .045			
	R^2 Adjusted	Adjusted R^2 = .013				Adjusted R^2 = .013				Adjusted R^2 = .014			
Effect size	Cohen's f^2	f^2 = .046				f^2 = .046				f^2 = .047			

***p < .05, **p <0.01**

Table H. The MR relationships between the predictors and the PALFAMS memory outcome [accuracy i.e. number of hits]

SUBTEST	PAL (hits)	Model 16: Maternal Gestational Drinking N=456				Model 17: Maternal Current Drinking N=462				Model 18: Maternal Past Drinking N=456			
Categorical variable	Category Coefficients	*B*	*SE*	*95% CI*	*β*	*B*	*SE*	*95 % CI*	*β*	*B*	*SE*	*95% CI*	*β*
Constant	Intercept	**11.91****	.74	10.46, 13.36	.	**11.87****	.74	10.42, 13.32	.	**11.87****	.75	10.40, 13.33	.
Area	De Doorns												
	Piketberg	-1.30	.67	-2.62, .03	-.14	-1.11	.68	-2.45, .23	-.12	-1.28	.68	-2.61, .05	-.14
	Grabouw	.37	.68	-.97, 1.71	.04	.50	.69	-.86, 1.86	.05	.37	.69	-.98, 1.72	.04
Residence	Non-Farm												
	Farm	-.63	.52	-1.66, .39	-.07	-.59	.52	-1.62, .43	-.06	-.61	.52	-1.64, .41	-.07
Home Language	Afrikaans												
	Non-Afrikaans	-.73	.63	-1.96, .51	-.08	-.89	.63	-2.12, .35	-.10	-.68	.63	-1.91, .55	-.08
Parental Marital Status	Married												
	Never Married	-.13	.47	-1.05, .79	-.02	-.11	.47	-1.02, .81	-.01	-.15	.47	-1.07, .76	-.02
	Other	.23	.60	-.95, 1.41	.02	.11	.60	-1.07, 1.28	.01	.23	.60	-.95, 1.40	.02
Household Size	2-4 Members												
	5-6 Members	-.15	.48	-1.08, .79	-.02	-.15	.47	-1.07, .77	-.02	-.19	.47	-1.11, .74	-.02
	7+ members	-.16	.56	-1.26, .94	-.02	-.13	.56	-1.23, .97	-.01	-.16	.56	-1.26, .94	-.02
Child Sex	Female												
	Male	-.21	.41	-1.01, .59	-.02	-.10	.41	-.90, .70	-.01	-.21	.41	-1.01, .59	-.03
Child age	9.0 – 10.12												
	11.0 – 12.12	.77	.49	-.19, 1.72	.08	.91	.48	-.03, 1.86	.10	.75	.48	-.20, 1.70	.08
	13.0 – 15.12	.84	.55	-.23, 1.92	.09	1.00	.54	-.07, 2.06	.10	.84	.55	-.23, 1.92	.09
Maternal Education	≥ Secondary												
	<=Primary	.24	.44	-.62, 1.10	.03	.12	.43	-.73, .97	.01	.21	.43	-.65, 1.06	.02
Maternal Employment	Employed												
	Unemployed	.05	.45	-.84, .94	.01	-.01	.45	-.90, .88	-.00	.08	.45	-81, 97	.01
Maternal (G/C/P) Drinking	No												
	Yes	-.43	.70	-1.80, .94	-.03	-.50	.74	-1.43, .43	-.05	.03	.47	-.90, .95	.00
Model Fit:	F statistic	F(14, 441) =1.01 Prob > F = .445				F(14, 447) =1.09 Prob> F = .364				F(14, 441) =2.36, Prob>F = 0.474			
	R^2	R^2 = .031				R^2 = .033				R^2 = .030			
	R^2 Adjusted	Adjusted R^2 = .000				Adjusted R^2 = .003				Adjusted R^2 = -.001			
Effect size	Cohen's f^2	f^2 = .032				f^2 = .034				f^2 = .031			

***p < .05, **p <0.01**

APPENDIX A: Ethics Approval

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

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

08 October 2018

HREC REF: 645/2018

Prof A Dalvie
School of Public Health & Family Medicine
Room 4.31, 4th floor
Falmouth Building FHS

Dear Prof Dalvie

PROJECT TITLE: MATERNAL ALCOHOL CONSUMPTION AND SOCIO-DEMOGRAPHIC DETERMINANTS OF NEURO-COGNITIVE FUNCTION OF SCHOOL CHILDREN IN THE RURAL WESTERN CAPE (SUB-STUDY LINKED TO 234/2009) Master's candidate - Ms P Viglietti)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

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

Approval is granted for one year until the 30 October 2019.

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

We acknowledge that the student: Ms Paola Viglietti will also be involved in this study.

Please quote the HREC REF in all your correspondence.

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

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

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

APPENDIX B: Child Development Author Guidelines

Society for Research in Child Development

Child Development Submission Guidelines

Description

Child Development invites for consideration manuscripts that are neither identical to nor substantially similar to work published or under review elsewhere. Editors retain the right to reject manuscripts that do not meet established ethical standards for research or dissemination.

Retrieved from: https://www.srcd.org/research/journals/child-development/child-development-submission-guidelines

Types of Manuscripts

Child Development considers manuscripts in the formats described below. Inquiries concerning alternative formats should be addressed to the Editor-in-Chief prior to submission. Most submissions (see below) are expected to be no more than 40 manuscript pages, including tables, references, and figures (but excluding appendices). With the exception noted below, if the submission is more than 40 pages, it will be returned to the author for shortening prior to editorial review. Note that we encourage extensive use of electronic supplements that do not count toward the page limit.

Empirical Articles comprise the major portion of the journal. To be accepted, empirical articles must be judged as being high in scientific quality, contributing to the empirical base of child development, and having important theoretical, practical, and/or interdisciplinary implications. Reports of multiple studies, methods, or settings are encouraged, but single-study reports are also considered. Empirical Articles will thus vary considerably in length, but should be no longer than 40 manuscript pages; text and graphics should be as concise as material permits. All modes of empirical research are welcome.

Brief Reports are reserved for short, cutting-edge empirical papers that are no longer than 4,000 words in length (including body text, tables, appendices, etc. but excluding references and electronic supplements), which advance research and knowledge in an area through noteworthy findings and/or new methods.

Reviews focus on past empirical and/or conceptual and theoretical work. They are expected to synthesize, analyze, and/or critically evaluate a topic or issue relevant to child development, should appeal to a broad audience, and may be followed by a small number of solicited commentaries. A large majority of the reviews accepted for publication at *Child Development* are meta-analyses or invited narrative reviews. Quantitative meta-analyses may be up to 50 pages in length to accommodate sample-specific detail.

Special Section is a format in which papers on a focal topic, written by different authors, are published simultaneously. In some cases, calls for submissions on particular topics will be disseminated through the SRCD (via e-mail or SRCD publications), and submissions will undergo normal editorial review. In some cases, a submitted manuscript (e.g., an Empirical Article) may be selected as a lead article for this format, with invited commentaries providing additional perspectives. The editors also welcome suggestions from readers for topics for this format.

Commentaries are peer-reviewed papers that respond to previously published *Child Development* papers. The original paper's authors have the option to submit a follow-up Commentary in response. Authors must note the paper of reference title, author list and, when available, DOI on the cover page at submission and cover letter. Paper titles are also set as "Commentary: [paper title]".

Sociocultural Policy

As developmental science becomes more global, and the role of context in human development becomes more evident, it is necessary that SRCD publications provide, in addition to age, an indication of the unique characteristics of the sample and the "socioeconomic and cultural place" from which their findings originate. Accordingly, it is now required that manuscripts to be published in SRCD journals specify clearly in the appropriate section(s) (e.g., Method, Discussion) and in an abbreviated form in the Abstract: (1) the dates of data collection (if applicable); (2) the theoretically relevant characteristics of the particular sample studied, for example, but not limited to: race/ethnicity, socioeconomic status, language, sexual orientation, gender identity (inclusive of non-binary options), religion, generation, family characteristics; and (3) the place(s) from which that sample was drawn, including country, region, city, neighborhood, school, etc. and all other context variables that are relevant to the focus of the publication, except when it violates expectations of privacy and confidentiality by an institutional review board or the setting itself. Additionally, selection and recruitment procedures should be clearly specified in the Method section.

The Sociocultural Policy is the product of a recognition that current policies and practices were not reflecting the state of the scholarship in terms of addressing diversity and replicability. As such, the Sociocultural Policy reflects current gaps in the science and is a dynamic policy. The Society will conduct ongoing reviews and re-evaluations of the Sociocultural Policy's effectiveness over time and its efficacy in advancing the Society's strategic goals. The Sociocultural Policy, procedures, and rationale will be revisited on a biannual basis to reflect changing demographics, an increasingly global society, and relevant contemporary issues.

Note for *Child Development* authors: In the adjudication of manuscripts, sociocultural generalizability or its absence will not be assumed on the basis of the demographic characteristics of a single sample. Instead, because sociocultural generalizability of scientific findings (or the lack thereof) is necessarily a product of direct comparisons across demographically diverse samples, *Child Development* encourages manuscripts reporting explicit comparisons of two or more groups to explore generalizability of key developmental phenomena, even if the focal phenomenon is generally regarded as well established in one cultural or other context. (Note that this should not be misconstrued as implying that *Child Development* does not publish studies based on single racial/ethnic groups, as the journal does publish such studies.) In addition, the editorial board of *Child Development* expects that the default position for quantitative (i.e., meta-analytic) reviews will be to include tabled information briefly describing key demographic features of the studies synthesized, along with explicit, even if exploratory examination of such key demographics (i.e., sex and ethnicity/race) as study-level moderators of the focal associations of interest. (This table, which should also minimally include effect size and reliability data for focal measures for each sample, may appear in supplementary, electronic materials.)

Formatting Requirements

The following points are requested of all papers submitted to *Child Development* and are required for any paper ultimately accepted for publication. Failure to comply with these requirements may lead to delays in processing, review, or publication. Failure to comply may also lead to the manuscript being returned to you for revision.

Format and Style

Child Development requires that all documents be submitted as Microsoft Word files (.doc or .docx; exceptions may be made by contacting the SRCD Editorial Office).

In addition, all manuscripts **must** align with APA Style rules including:

- Double-spacing throughout (abstract, body text, references)
- Using 12-point, Times New Roman font
- 1-inch margins
- When providing racial or ethnic designations, please follow APA's language guidelines. See the Publication Manual of the American Psychological Association (APA, 2001, pp. 75–76). Use initial capital letters (i.e., Black and White instead of black and white). Do not use the term Caucasian when describing Whites or people of European descent.

Page Limits

40 pages for Empirical Articles and Reviews, inclusive of everything aside from electronic supplementary materials. The reference list is included in the 40-page total, and may be 8 pages at most. (Quantitative meta-analyses may be up to 50 pages in length).

4,000 words for Empirical Reports, excluding title page, abstract, and references, but inclusive of body text, tables, figures, and appendices.

Manuscript Structure

Empirical Articles and Reports must have the following major sections (other article types may vary):

- Introduction (but not labelled as such)
- Method
- Results
- Discussion
- References
- Tables and Figures

The Method section **must** include participant demographic information, such as sex, SES, race or ethnicity, recruitment method, etc.

Abstracts

- Must be 120 words or fewer
- Include participants' numerical age
- Include total number of participants (*N*s)
- Should generally report the focal effect size(s), as appropriate
- Must be written in the third person, **not** first person

References

- Do not exceed 8 pages
- Are cited both in the body text and on the reference list
- Are listed in alphabetical order by authors' surname
- Include the DOI # when available

Figures

Color figures publish online for free, but there is a $325 cost to **print** in color. More technical information on images (accepted file types, image quality, etc.) is available at Wiley-Blackwell Author Services.

Footnotes and Endnotes

Child Development does **NOT** publish footnotes or endnotes of any kind. All such notes must be incorporated into the body text.

Blinding

Child Development uses a double-blind reviewing procedure. Please ensure any information that might identify authors is either removed or sufficiently masked.

Information such as the author list, affiliations, acknowledgements, etc. should be removed from the main manuscript file and uploaded as a separate Title Page file during submission.

In-text references to any work by the authors should be referred to in the third person to mask the authors' identities (for example: "We have shown in previous work that children...(Martin, 2011)" should instead be written as "It has been shown in previous work that children...(Martin, 2011)").

APA Style Reminders

Child Development follows the Sixth Edition of the Publication Manual of the American Psychological Association (APA).

The following are reminders of often forgotten points of APA style. However, ultimately it is the author's responsibility to comply with APA regulations. Failure to follow APA rules may lead to delays in the production process and the publication of your manuscript.

Sexism
Avoid sexist language; use plural phrases such as "children and their toys" rather than "a child and his toy." Refrain from referring to children with "it."

Figures
Please keep figures as clear and simple as possible. For example, do not use a three-dimensional bar graph unless you are presenting data along three dimensions. Be sure that labels are large enough to be visible when the figure is reduced in size. Remember to provide figure numbers and captions separately, not on the figure itself. Individual figures must be in EPS, PDF, PNG, or TIFF format, with resolution of at least 300 dpi.

"Relationship" vs. "Relation"
These are not interchangeable. "Relationship" is used to describe a social bond, such as between a mother and a child, a teacher and a child, etc. "Relation" is used to describe non-animate associations, including those between variables.

Uses of Slash (/)
Uses of slash in the abstract and body text must be avoided. Examples include "and/or," his/her," etc. "His/her" can (and should) be written as "his or her." Slashes may be used in references, tables, and figures. Slashes may also be used when citing previously written material, such as including in the paper a test question that was used with participants.

Note: Online Supplementary Materials

Child Development is able to host supplementary materials to articles published in the journal on its Wiley Online Library website. The current editorial team has been encouraging authors to take advantage of this resource as a way to cut the amount of material included in print articles and to provide additional information to interested readers. As such, we are urging authors to look critically at their manuscripts to find information that could potentially be moved online. Examples of such materials include extra tables, figures, or appendices; test questions or other test materials; videos of experiments taking place; or additional data sets from meta-analyses. For Wiley's guidelines for online supporting materials please see http://olabout.wiley.com/WileyCDA/Section/id-828014.html.

Additional Requirements

Prior Publication/Preprints

Submitted manuscripts must not have been published elsewhere. In general, preprints (e.g., on a departmental website, on PsyArXiv) will not count as prior publication. However, if the document has a copyright license (including Creative Commons), or any other constraints on editing or publication of the work, this information must be disclosed and addressed in the cover letter. **It is the responsibility of authors to provide sufficient information about publicly available versions of the manuscript to allow editors to make informed decisions about prior publication**.

Please note that once a manuscript is accepted for publication, SRCD policy requires that any previous versions be labeled as “drafts” or “working papers.” There must be some designation indicating that those documents are not “the version of record.” If restrictions on prior versions preclude editing to add this designation, SRCD will likely be unable to accept the submission.