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2017

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Factors Influencing Early Childhood Neurodevelopment:

Evidence from the Birth to Twenty Cohort

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A research report submitted to

the Faculty of Health Sciences, University of the Witwatersrand,

in partial fulfilment for the degree of Master of Medicine in Paediatrics

Johannesburg 2016

DECLARATION

I, Jessica Katharine Rule declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in Paediatrics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signed,

Jessica K Rule

The ……day of ……., 2016

DEDICATION

I dedicate this work to my parents, Stephen and Susan Rule, who have dedicated their lives for the benefit of their family. I also dedicate this work to my husband, Christopher Strong, because without his support, it would not have been possible.

ABSTRACT

Introduction

Neurocognitive development in early childhood is a complex process with multiple genetic and environmental influences. The Birth to Twenty study conducted neurocognitive assessments of children at 1- and 5 years of age using the Griffiths Mental Development Scale (GMDS) and the Denver Prescreening Developmental Questionnaire (DPDQ) respectively. The current study examined the effects of breastfeeding until the age of 6 months, childhood linear growth, household asset index, maternal parity, maternal level of education, and maternal depression on children's neurocognitive development.

Objective

The primary objective of the study was to investigate the associations between various sociodemographic factors with both the GMDS and the DPDQ. The secondary objective was to examine each of the sociodemographic factors across different cognitive developmental patterns among children between 1- and 5-years of age.

Method

The study used historical data from the Birth to Twenty **longitudinal cohort** study. Secondary data analyses were used to examine the associations between **the selected** sociodemographic factors and cognitive development scores. The childrens' performance on the GMDS and the DPDQ were divided into tertiles in order to examine the role of each **selected** factors on the GMDS and DPDQ.

Results

Findings revealed significant associations between linear growth at 2 years of age and both the GMDS ($r = 0.20$, $p = 0.036$) and the DPDQ scores ($r = 0.21$, $p = 0.034$), maternal parity and

the DPDQ score *(r = -0.16; p= 0.041)*, and maternal education and the DPDQ score (*F(1,166) =15.92, p<0.001).* **Linear growth and maternal education differed significantly in cognitive development tertile groups, but these results were unexpected and of uncertain significance.**

Conclusion

This study has shown the expected positive effect of higher levels of maternal education, better linear growth **at age 2 years** and lower maternal parity on early childhood neurocognitive development in **predominantly** black South African children. It did not find the expected associations between neurocognitive development and household demographics, breastfeeding and maternal depression. More research in this field **is required**.

ACKNOWLEDGEMENTS

I gratefully acknowledge and thank:

- Almighty God for granting me the strength and the perseverance to commence and complete this research project.
- My supervisors, Dr Celia Hsiao and Professor Lorna Jacklin.
- All the children and their families whose data contributed to this study.
- The Medical Advisory Committee and the MRC/Wits Developmental Pathways for Health Research Unit for allowing me to conduct this study.

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ACRONYMS

ANOVA: Analysis of variance

Bt20: Birth to Twenty

DPDQ: Denver Prescreening Developmental Questionnaire

fMRI: functional magnetic resonance imaging

GMDS: Griffiths Mental Development Scale

GQ: General Quotient

HAZ: Height for age z-score

HIV: Human Immunodeficiency Virus

HSD: Honest significant difference

IQ: Intelligence Quotient

LAMIC: Low and Middle Income Countries

PDI: Pitt Depression Inventory

PUFA: Polyunsaturated fatty acids

SD: Standard deviations

SE: Standard error

1.0 Introduction

The development of the brain is a complex and not fully understood process. Although neurodevelopmental sequences are genetically determined, it has been established that biological and psychosocial factors associated with poverty adversely affect early childhood neurocognitive development. The implications of poor early childhood neurocognitive development are far-reaching, influencing schooling and adult productivity. It is estimated that 200 million children younger than 5 years are not attaining their developmental potential in the developing world.[1] Identifying factors that adversely affect neurocognitive outcomes in these children is essential not only to the individual but also to alleviate the cycle of poverty in which they live. This research project therefore examined the correlates of neurocognitive development in Sowetan children in the 1990s.

1.1 Literature Review

Neurodevelopmental Assessment in South Africa

There is limited data on patterns and factors influencing neurocognitive development in South African children. The measurement tools available for assessing early childhood neurocognitive development are created, validated and frequently used in high-income countries. These tools are typically administered by trained professionals, rely on excellent communication between the administrator and the child and parent, and often depend on parent recall. These instruments are often modified and used in low and middle income countries (LAMIC) such as South Africa. Whilst in high income countries, there are large bodies of evidence examining the influence of various biological and psychosocial factors on children's early cognitive development, as well as the mechanisms underlying the complex process of early childhood neurocognitive development; there is limited data in low and middle income countries such as South Africa. South African evidence is thus critical to

understand patterns of and factors influencing neurocognitive development, in order to inform South African policy on early childhood neurocognitive development.

The Birth to Twenty (Bt20) cohort study enrolled 3273 children born in Soweto in 1990 and followed them up to twenty four years of age. It was initiated during the changing political climate as the Apartheid regimen in South Africa was crumbling, and rapid, unorganised urbanisation was anticipated. It was excepted that this urbanisation would have profound effects on children's' health and development.[2] **Data measured included antenatal information** about the pregnancy, growth, health, family socio-demographics, well-being and educational progress of participants and their families **as well as a focus on factors influencing early cognitive neurodevelopment, performing two neurocognitive assessments on the enrolled children[2].** The study administered two instruments to assess children's cognitive development, the Griffiths Mental Development Scale (GMDS) when participants were 1 year of age, and the Denver Prescreening Developmental Questionnaire (DPDQ) when participants were 5 years of age[2]. Bt20 is one of five longitudinal birth cohort studies in LAMIC and forms part of the the Consortium of Health-Oriented Research in Transitioning Countries (COHORTS)**; it represents a unique database because of both the population that it studies as well as the sociodemographic and neurodevelopmental data available[62].**

<u>The Griffiths Mental Development Scale</u>

The Griffiths Mental Development Scales (GMDS) [3] are comprised of six sub-scales: locomotor, personal-social, hearing and language, eye and hand co-ordination, performance and practical reasoning. Sub-scales are tabulated to form an overall total score. The GMDS is the most extensively used neurodevelopmental tool in South Africa[4-9] however population specific norms have yet to be established. When GMDS scores of "normal" black South African children

between 13 and 16 months of age were compared to the 1996 British norms, South African children achieved higher scores in the hand-eye co-ordination and performance scales while the British children performed better in the personal-social scale.[9] A study in 2001 examined the construct validity of the GMDS and found that the items tested in each sub-scale relied on multiple constructs, suggesting that restructuring of the sub-scales would produce more meaningful results. Furthermore the study raised concerns about employing the GMDS in the South African context, especially on the personal-social sub-scale as this scale is particularly sensitive to cultural norms.[5] However, the GMDS is used widely in South African studies[4-9]. Laughton et al found normal GMDS scores in 11-month old infants which declined over time in children from low socio-economic backgrounds.[7] Laughton et al also used the GMDS to assess neurocognitive development in children with Human Immunodeficiency Virus (HIV) and found that neurodevelopmental delay associated with HIV was improved to almost normal by early commencement of antiretroviral treatment.[6] Davies et al assessed neurocognitive development in children with foetal alcohol syndrome using the GMDS and found significant developmental delay in these children[8]. Evidence thus exists that the GMDS is a useful and valid tool in the South African context.

The Denver Prescreening Developmental Questionnaire

The Denver Prescreening Developmental Questionnaire (DPDQ) and the revised-DPDQ are parent-report instruments aiming to identify children at risk for neurodevelopmental delay and who will require further screening and neurodevelopmental intervention. Its advantages are that it is cost-effective, does not require extensive expertise and can be performed quickly, **however there are concerns about its sensitivity and positive predictive value**.[10, 11] Luiz, et al compared the GMDS to the DPDQ in Xhosa-speaking South African children and found that the children performed better on the GMDS than on the DPDQ, possibly suggesting that the DPDQ is more sensitive than is necessary. The study also suggested that for the DPDQ,

children's performance was poorest on the personal-social sub-scale, and that these items may have been culturally inappropriate.[12] The DPDQ used in the Bt20 cohort adapted some of the items in order to render the assessment more culturally appropriate. For instance, the item 'What is a hedge?' was changed to 'What is a fence?' as children in this context would be more familiar with a fence than with a hedge.[13] Such modifications were necessary to prevent children from under-scoring in the assessment due to cultural misunderstanding rather than true cognitive delay.[13, 14]

Factors Influencing Neurocognitive development

Breastfeeding

The benefit of breastfeeding of young infants is well documented. Breastfeeding has been shown to reduce mortality owing to infectious disease in developing countries.[15] The Cochrane Review in 2012 published data showing that breastfeeding reduces the risk of gastrointestinal and respiratory tract infections in infants, promotes maternal weight loss and prevents recurrent pregnancy in mothers.[16]The World Health Organisation promotes exclusive breastfeeding to six months of age, and thereby limits randomisation of infants to exclusive formula-feeding groups in randomised controlled trials. Therefore the evidence for neurodevelopmental benefit of breastfeeding is riddled with issues, as most systematic reviews are retrospective, have small sample sizes and do not adequately adjust for confounding factors, including socio-economic status and maternal Intelligence Quotient (IQ). [17-24] The question as to whether breastfeeding independently confers neurodevelopmental advantage to children, or whether confounding factors associated with a breasted child's environment are responsible for improved neurodevelopmental outcome is topical. **A secondary, yet unanswered, question is whether the duration or exclusivity of breastfeeding confers the most benefit, or whether or not this neurodevelopmental benefit is dose-dependent.**

The Millennium Cohort Study (2005) enrolled 18 500 infants in the United Kingdom, taking into account socio-economic status, infant health status, household composition and adult-child interaction and examined the association between breastfeeding and neurodevelopmental outcomes. The study found that the proportion of infants who attained their developmental milestones at 9 months of age increased with duration and exclusivity of breastfeeding.[17] This not only supports the positive association between improved neurodevelopmental outcomes and breastfeeding, but also suggests that this association is dose-dependent. The Cochrane Review found that breastfed infants crawled significantly earlier and that there was and a trend towards earlier sitting compared to formula-fed infants, suggesting some association between breastfeeding and gross motor milestones.[16] This finding is confirmed by a Spanish cohort of breastfed infants attaining higher neurodevelopmental scores at 14 months of age than formula fed infants, with results adjusted for social, psychological and nutritional factors.[25] A cohort of 22 399 of infants enrolled in a prospective study in the United States, found that mothers of breastfed infants had fewer concerns about the achievement of language and motor development than mothers of formula fed infants.[26] Therefore there is a growing body of evidence suggesting that breastfeeding is independently associated with improved neurodevelopmental outcomes and steps have been made to eliminate the effect of confounding factors that may otherwise explain the association.

A prospective study in Poland using neurodevelopmental information of children up to the age of 7 years found that the higher IQ scores attained by 1-year old breastfed infants were also sustained at 7-years, supporting the long term influence of breastfeeding on children's cognitive development.[27]

The exact mechanism for the neurotrophic effect of breast milk itself is not fully understood. Breast milk contains fatty acids and micronutrients which are known to aid in neurodevelopment. Docosahexaenoic acid and arachidonic acid which are found in human breast milk but are absent in formula and cow's milk have been shown to improve eyesight and cognitive ability.[27] A Spanish study in 2011, the first of its kind, investigated the concentration of various polyunsaturated fatty acids (PUFA) in maternal colostrum to determine if there was a correlation between the achievement of neurodevelopmental milestones and a particular PUFA. The study found that there were improved neurodevelopmental outcomes in infants who received breast milk with higher levels of n3-PUFA, including docosahexaenoic acid. This effect was strengthened with an increased duration of breastfeeding.[28] A review published in 2014 in the Nutritional Journal hypothesises that improved nutritional supplementation of infant formulas may improve neurodevelopmental outcome in pre-term infants.[29]

Emerging evidence in the field of neuro-imaging contributes to our knowledge of the mechanism underlying the influence of breastfeeding on neurodevelopment[30]. Deoni et al published a study in 2013 showing increased white and grey matter volumes as well as increased parietal lobe thickness associated with increased IQ in adolescents who were breastfed as compared to those who were formula fed.[30] This study attempted to eliminate bias by correcting for socio-economic status and maternal education level as a surrogate for maternal IQ. Other confounding factors that were accounted for were using only singleton pregnancies, with Apgar scores of at least 8, no history of head trauma, no intensive care unit admissions, no family history of neurological or psychological illness, no complications or illicit drug use during the pregnancy. The findings of this study seem to support the hypothesis of the neurodevelopmental effect of breastfeeding, and seeing this benefit into adolescence. However the inferences made in this study between breastfeeding, increased

white matter volume and intelligence have been criticised[31]. It is possible that the differences in white matter volume may be explained better by premature introduction of cow's milk in the formula fed groups as opposed to the breastfed groups[31]. The counter-hypothesis is that the avoidance of cow's milk in early childhood is the factor that confers the neurodevelopmental benefit and not the breast milk itself.[31]

Linear Growth

Malnutrition is a significant problem worldwide, with an estimated 165 million children under the age of 5 years being classified as stunted in 2011, with the vast majority of these children living in the developing world.[31] Stunting is defined as height **for age of two standard deviations below the median[32]** and has been associated with poor cognitive development[14, 33-36] during the first two years, occurring frequently in developing countries owing to multiple factors. As breastfeeding becomes insufficient to support rapid growth at about 6 months of age, poor complementary feeding practices, recurrent infections, exposure to toxins and poor infant nurturing lead to malnutrition which is marked by impaired linear growth.[32] Although stunting itself is associated with neurodevelopmental delay, stunting occurs within a setting of low socio-economic status, inadequate stimulation and low levels of parental education**[33-36].** These confounding factors must be considered when investigating the relationship between stunting and neurodevelopment.

Many studies have found that stunting is independently associated with poor neurodevelopmental outcomes[33-36]. A cross-sectional study in Burkina-Faso found that stunting was associated with motor, language and personal-social developmental delay.[36] A Peruvian study published in 2002 followed children into late childhood and found a significant correlation between stunting at the age of 2 and cognitive deficit at the age of 9, and this association was independent of other diarrhoeal diseases.[34] In a review of birth cohorts from

five developing countries, Martorell et al found that weight gain in the first two years of life was more important than weight gain after two years of age in predicting schooling outcome.[33] This was supported by the World Bank Economic Review study which found that nutrition in the second year of life is the most significant in predicting neurodevelopmental outcome.[37] It is hypothesised that the cognitive deficit inflicted by stunting at age 2 is ameliorated if there is significant catch-up growth by 5 years of age.[33]

A possible neurobiological mechanism explaining the association between stunting and cognitive development could be the inflammatory processes, which are initiated when a child enters a malnourished physiological state. Both the nutritional deficiency and the inflammatory processes can be implicated in impaired neuronal differentiation and maturation[38], which result in global neurodevelopmental delay. There is a growing body of evidence on the impact of stunting on neurodevelopmental outcome, and it is an essential factor to consider when profiling neurodevelopmental patterns.

Household Demographics

Caregiver income can only partially serve as an indicator of socioeconomic status because it may not reflect household income, and household income may vary widely if the members of the household work in informal economy as traders for instance. For this reason, studies in low and middle income countries generally use household assets as an index of socioeconomic status[38]. This approach has been frequently used in the literature[39, 40].

A topical study published in Pediatrics in 2008 found an association between energy insecurity and increased neurodevelopmental delay.[41] It suggested that with decreased access to electricity, owing to rising costs of petroleum and energy resources, the ability of low-

income households to sustain safe and healthy environments for their children decreased. A study published in Cape Town found that the GMDS scores of children from low socioeconomic backgrounds decreased significantly between 11 and 21 months of age, suggesting a detrimental effect of low socioeconomic status in the critical second year of neurodevelopment.[7]

Recent data published in Nature Neuroscience found that the surface area in the brain was proportionate to household income and that this discrepancy was most marked in children of low socioeconomic status.[42] It was found that the deficits in surface area in children from low income families affected predominantly areas of the brain that are thought to be involved with language, reading, and executive function spatial skills. This evidence is supported by functional magnetic resonance imaging (fMRI) showing lower levels of prefrontal neuronal activity in children from low-income families.[42]

Therefore as poverty is undoubtedly a significant problem in South Africa, and its effect on the rapidly developing brain has been documented, this study will aim to add to the evidence in a South African context, with the hope of highlighting the importance of promoting the best possible environment for South African children to develop neurologically.

Maternal Education

Maternal education, as outlined by the Millennium Development Goals[43], should be prioritised in the developing world. Early childhood neurodevelopment is influenced not only by nutrition and home environment, but also by appropriate stimulation at home[13]. It is thought that higher levels of maternal education increase the propensity to a safe and nurturing home environment, and provide the mother with greater resources to use in interaction with and stimulation of her child[44, 45].

The Rhea study in Greece also found maternal education level to infer the greatest benefit to neurodevelopment at 18 months of all the psychosocial factors measured.[44] This finding is supported by a small Johannesburg study which found that maternal level of education was associated with higher overall scores and higher gross-motor scores on the GMDS.[45] A South African study has shown that higher levels of maternal education attenuated initially poorer neurodevelopment milestone achievement at 1 year by an assessment made at 5 years of age. [13] This finding suggests that the protective effect of maternal education modifies a poor neurodevelopment trajectory, highlighting this modifiable factor perhaps above all other factors.

Higher maternal education is likely to foster a healthier and safer home environment, better health behaviours, greater access to services, higher quality of child care and higher levels of infant stimulation.[46, 47] Mothers who have higher levels of education may also have access to greater intellectual resources with which to stimulate their children, and to interact with their children with greater verbal responsiveness by asking them questions, providing guidance and scaffolding, and involving them in learning activities such as book reading[44] all of which provide the type of home stimulation that contribute significantly to children's cognitive development.

Maternal Depression

Both pre- and postnatal maternal depression are not only detrimental to the mother, but have significant consequences in terms of the child's neurodevelopment. [48,-51] A recent South African study showed that the prevalence of maternal postpartum depression in a South African township was 31.7%.[48] Despite such high rates of maternal postnatal depression, studies examining its impact on child neurodevelopment in South Africa are limited.

A recent neuroimaging study found significantly lower fractional anisotropy and axial diffusivity in the right amygdala of infants exposed to maternal pre-natal depression.[49] This suggests changing neuronal interactions which seem to be related to neurobiological factors and not only decreased stimulation postnatally. A study in the United States suggests that it is the prenatal activation of the hypothalamic-pituitary axis that infers insult to the neurodevelopment process.[50] There is suggestion that prenatal maternal depression results in abnormal neural programming which results in abnormal neurodevelopment persisting at least into adolescence.[51]

A literature review published in 2007 found that there was a significant association between maternal perinatal depression and neurodevelopmental problems. This review found that prenatal depression independently predicted poorer neurodevelopmental outcomes, when both postnatal depression and anxiety were taken into account.[50] The Rhea study supports these findings, and additionally proposes that postnatal depression predominantly affects cognitive and fine-motor development. [52] A review of the literature from developing countries found that children from depressed mothers were at increased risk of stunting[53] and this growth faltering is known to be associated with neurodevelopmental delay.[34, 54-56] A South African study found that postnatal depression doubled a child's risk of neurocognitive problems at the age of 10 years.[57]

Maternal Parity

Lastly, greater maternal parity has been shown to have an adverse impact on childhood neurodevelopment[44] and is taken into account when considering factors influencing neurodevelopmental outcomes. Having one or more older sibling(s) at home may reduce the

mother's attention, emotional availability, and resources, and hence have a significant influence on the child's home environment[44].

Justification for this research project

As outlined in the Millennium Development Goals focusing on mother and child health and aiming to achieve universal primary education, it is clear that improving our understanding of the factors influencing early childhood neurodevelopment in South African children is an important goal [43] The assessment of neurodevelopment is particularly difficult in South Africa owing to the limited applicability of internationally developed assessment tools and lack of locally designed and developed instruments. There is a wealth of evidence from high income countries on the impact of breastfeeding, linear growth, household demographics, maternal education, maternal depression and maternal parity on the neurodevelopment of a child, but a paucity of evidence exists in LAMICs. The availability of early childhood neurodevelopment assessments which were adapted to suit the local South African context, as well as various child, maternal, and socio-demographic information in the Birth to Twenty study, assessed within a longitudinal framework, can contribute significantly to our current knowledge of the factors influencing early childhood neurodevelopment in South Africa.

The aim of this study is twofold: first, to examine the influence of a host of maternal and sociodemographic factors (exclusive breastfeeding, linear growth, household demographics, maternal education, maternal depression, and maternal parity) on early childhood development in South Africa; and second, to profile neurocognitive development patterns in South African children between 1 and 5 years of age. Results from this study provide a basis for further research on children's cognitive development and can have significant implications in the design of interventions to improve childhood neurodevelopmental outcomes in South Africa.

1.2 Hypothesis and Objectives

Based on the extant literature, it is expected that breastfeeding, adequate linear growth, higher household income, higher levels of maternal education, lower levels of maternal depression and lower maternal parity would have a positive association with children's neurocognitive development at both 1 and 5 years of age.

Primary Objective

To investigate the associations between each of the following variables with children's scores on the Griffiths Mental Development Scale (GMDS) at year 1, and Denver Prescreening Developmental Questionnaire (DPDQ) scores at year 5:

1. **Breastfeeding at 6 months**
2. Child linear growth
3. Household asset index
4. Maternal level of education
5. Maternal Pitt depression Inventory
6. Maternal parity

Secondary Objective

To profile neurocognitive development patterns in South African children between 1 and 5 years of age.

<u>Study Design</u>

This study is based on **secondary analysis of longitudinal cohort data from the Birth to Twenty study**. These data included:

GMDS (measured at 1 year)

DPDQ (measured at 5 years)

Breastfeeding at 6 months

Child height for age z-score (measured at 2 years)

Household asset index (assessed between 0 and 2 years)

Maternal level of education (assessed at birth)

Maternal parity at birth (assessed at birth)

2.0 Methodology

2.1 Participants and setting

Soweto is an urban township covering 108 square kilometers south west of Johannesburg. The Bt20 study was based in Soweto, Johannesburg and included all singleton children born to mothers between 23 April and 8 June 1990.[2]

2.2 Measures

Griffiths Mental Development Scale (GMDS)

The GMDS consists of five sub-scales: locomotor, personal-social, hearing and speech, eye-hand co-ordination, and the performance scale. The current study used the General Quotient (GQ), which is a sum of the five subscale quotients, and is frequently used as a measure of children's cognitive development at 1 year of age.[13]

Denver Prescreening Developmental Questionnaire (DPDQ)

The revised DPDQ employed by Bt20 involves 32 items covering the child's personal-social, fine-motor, gross motor and language abilities. It includes tasks such as hopping on one foot, drawing shapes, defining words and a rating of the child's speech. Children's scores on the DPDQ are age-adjusted. Some items were adapted to make them more culturally appropriate, and to avoid children's underperformance caused by language and cultural barriers. **It is administered in the participant's home language and the instrument includes both direct observations and the caregiver report**[14]

Breastfeeding

Feeding choice in the Bt20 cohort was assessed through a questionnaire administered to mothers when children were 6 months of age. The questions included in the current analysis are, "Have you ever breastfed this baby?", "Are you still breastfeeding this baby?", and "At what

age was the baby when you started this (introduced bottle feeds?)". Mothers' responses were categorised into those who were breastfeeding at six months of child age, and those who were not.

Linear Growth

Child linear growth was indexed by the height-for age Z-score (HAZ) at 2 years of age. As defined by the WHO, stunting is assessed when a height is more than 2 standard deviations (SD) below the median height for a child's gender and age. [58] Children were classified as stunted when the height for age z-score was less than -2SD, and not stunted, when the height for age z score was more than -2SD.

Household Demographic

The household asset index was obtained when children were between 0 and 2 years of age. The score was based on the family's ownership of; electricity, a television, a radio, a motor vehicle, a fridge, a washing machine and/or a telephone. Ownership of assets was summed with the total household asset score ranging from 0 to 7.

Maternal Education

Maternal education was assessed when children were 2 years of age. Mothers were asked their highest standard of school passed. The results were categorised into mothers attaining a level of education below a Standard 8 level, and those above a Standard 8 level.

Maternal **Postnatal** Depression

Maternal perinatal depression was assessed using the Pitt Depression Inventory (PDI) when the children were 6 months old. The PDI comprises of 24 questions pertaining to current maternal mood, attitudes and behaviour. Mothers' answers, which ranged from 0 to 2 for each

question, were coded and summed. Of a possible maximum score of 48, mothers who scored above 19 were classified as being affected by postpartum depression.[59] The PDI has been used widely and has been shown to correlate closely with the Edinburgh Postnatal Depression Scale.[60]

Maternal parity

Mothers were asked 2 questions antenatally: "Have you been pregnant before", and if yes, "Please give the details for each pregnancy" including date of birth, mode of delivery, sex, gestational age and current health. From these data maternal parity was ascertained.

2.3 Statistical analysis

Primary objective: To investigate the associations between maternal and demographic variables with children's scores on the Griffiths Mental Development Scale (GMDS) at year 1, and Denver Prescreening Developmental Questionnaire (DPDQ) scores at year 5.

Associations between the continuous variables, including the HAZ, household asset index, maternal PDI and maternal parity with the GMDS and the DPDQ were determined using a Pearson's correlation. Associations between categorical variables, including maternal feeding choice, stunting and maternal education, and the outcome variables were determined through an Analysis of Variance (ANOVA).

Secondary objective: To profile neurocognitive development patterns in South African children between 1 and 5 years of age

Maternal and sociodemographic variables were compared across children's cognitive development profile from 1 to 5 years. To establish children's profile in early cognitive development, four groups of children were identified:

1. Those who performed in the top tertile of both the GMDS and the DPDQ
2. Those who performed in the top tertile of the GMDS but in the bottom tertile of the DPDQ
3. Those who performed in the bottom tertile of the GSMD but in the top tertile of the DPDQ
4. Those who performed in the bottom tertile of both the GSMD and DPDQ

Next, continuous background variables (parity, maternal PDI, HAZ and household asset index) were compared across the 4 profile groups through a one-way ANOVA. The categorical variables (maternal feeding choice, stunting and maternal education) were compared across the 4 groups using Chi-square tests.

2.4 Ethical Considerations

Permissions for the study were obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (see Appendix 1) and the MRC/Wits Developmental Pathways for Health Research Unit (see Appendix 2).

The Birth to Twenty cohort runs in conjunction with a community advisory board which is consulted if any ethical concerns are raised for the duration of the study. Staff involved in the cohort undergo Good Clinical Practice and ethical research conduct training. The Bt20 was initially funded by the Medical Research Council, but as it developed gained other seed

funding. Participants in the cohort are compensated for transport, and when necessary are provided with a limited social and medical referral service.[2]

3.0 Results

3.1 Study Group Characteristics

The cohort enrolled 3273 of the 5449 children born during this 7-week period. The attrition rate at follow up has been approximately 30%, which is on par with birth cohorts in other developing countries[1]. The children lost-to-follow-up tended to be children from wealthier white families. The current analysis included only those children who had complete data on both the GMDS at 1 year and the DPDQ at 5 years. The resulting sample size for the study included 167 participants (89 boys and 78 girls). The mean age at which the GMDS was performed was 1.14 years (*M* = 0.95; 1 *SD* = 0,33) and the DPDQ at 5.23 years (M = 4,96; SD = 6.18). **The study sample did not differ significantly from the rest of the cohort with available data in terms of household assets *F*(1, 2858) = .27, *p* = .603 and maternal education Chi-Square (5, N=2932) = 4.105, *p* = .534.** Participant demographic information is presented in Table 1.

Table 1: Characteristics of the study group

	N (%)
Gender	Boys 89 (53.3)
Ethnicity	Black 166 (99.4) Coloured 1 (0.6)
Marital Status	Married 41 (24.6) Living together 1 (0.6) Single n=125 (74.9)
	Mean (SD), Range
Birth weight (kg)	3.14 (0.43), 1.77 ~ 4.15
Maternal age (years)	24.45 (5.74) 16~42

3.2 Neurocognitive measures

The results of the GMDS and DPDQ are shown in Table 2.

Table 2: GMDS and DPDQ scores

	Mean (SD), Range
GMDS Total Score	106.67 (12.00), 52.53~144.88
DPDQ age adjusted Score	43.62 (4.11), 23.92~50.74

3.3 Maternal and Sociodemographic factors

The maternal and sociodemographic factors are demonstrated in Table 3.

Table 3: Descriptive statistics of maternal and sociodemographic factors

Measure	***Categories***	***N (%)***	***Total***
Breastfeeding at 6 months	Yes	97 (84.3)	N=115
	No	18 (15.6)	
Maternal Education	Completed Std 8	90 (53.9)	N=167
	Completed matric or post matric studies	77 (46.1)	
Stunting	Height for age z-score <-2SD	14 (13.1)	N=107
	Height for age z-score >-2SD	93 (86.9)	

	Mean (SD), Range	***Total***
Household Asset Index	3.98 (1.246), 0 ~ 7	N=167
Maternal PDI	15.31 (7.341), 2 ~ 42	N=113
Maternal Parity	1.94 (1.269), 1 ~ 8	N=167
HAZ	-0.98 (0.917), -3.9 ~ 1.43	N=107

3.4 Influence of Maternal and Sociodemographic factors on neurocognitive measures

Household asset index was not significantly associated with the GMDS (r = -0.24, p = 0.168) but was positively correlated with the DPDQ (r = 0.14, p = 0.076). Maternal PDI was negatively correlated with both the GMDS (r= -0.03, p = 0.738) and DPDQ (r= -0.07, p = 0.436). Maternal parity and the DPDQ were negatively correlated but this was only marginally significant (r = -0.16, p = 0.041). Height for age z-score was significantly associated with the GMDS (r = 0.20, p = 0.036) and the DPDQ (r = 0.21, p =0.034). Children who were breastfed at 6 months did not differ significantly from children who were not breastfed at 6 months on both the GMDS (F(1, 204) = 1.34, p = 0.821) and DPDQ (F(1, 114) = 0.03, p = 786). Compared to children whose mothers completed only a Standard 8 level of education, children of mothers who finished matric or further studies performed significantly better on the DPDQ (F(1,166) =15.92, p=0.000). There was significant difference in the mean DPDQ between the stunted (HAZ < -2) and non-stunted (HAZ > -2) groups (F(1, 106) = 4.58, p=0.038). ANOVA analysis was not performed on GMDS and HAZ as the outcome was measured before the variable. See Tables 4 and 5.

Table 4: Correlations between continuous variables and GMDS and DPDQ

	GMDS (p)	***DPDQ (p)***
Household Asset Index	-0.24 (0.168)	0.14(0.076)
Maternal Pitt Depression Inventory	-0.03 (0.738)	-0.07 (0.436)
Maternal Parity	-0.03 (0.912)	-0.16 (0.041)
Height for age z-score	0.20 (0.036)	0.21 (0.034)

Table 5: One way ANOVA between categorical variables and GMDS and DPDQ

	GMDS (p)			DPDQ (p)		
	Mean	***SE***	***F***	***Mean***	***SE***	***F***
Breastfed at 6 months	106.78	0.83	1.34	43.83	0.45	0.03
Not breastfed at 6 months	104.11	3.05		43.65	0.80	
Completed Std 8	106.03	0.87	0.84	42.49	0.47	15.92***
Matric/graduate	106.87	1.20		44.93	0.37	
HAZ <-2				42.15	1.18	4.58**
HAZ >-2				44.43	0.36	

*p<0.1, **p<0.05, ***p<0.001

3.5 Maternal and sociodemographic factors across cognitive development profiles from 1 year to 5 years of age

Participants were divided into four groups to determine the influence of the maternal and sociodemographic factors on children's neurocognitive developmental trajectory.

Results from a one-way ANOVA comparing the continuous variables across all 4 groups showed that household asset index varied significantly between the 4 groups ($F(3,73) = 2.31$, $p = 0.063$, df = 3). Tukey's HSD posthoc analyses indicated that the household asset index score was higher for children in group 2 (children who performed in the top tertile of the GMDS but in the lowest tertile of the DPDQ) than children in group 1 (children who performed in the top tertile of both the GMDS and the DPDQ) ($p = 0.068$). Maternal parity also varied across the four

groups ($F(3, 73) = 2.32$, $p = 0.072$, df = 3). Children in group 3 (who performed in the lowest tertile of the GMDS but the top tertile of the DPDQ) had fewer siblings than children in group 1 (children who performed in the top tertile of the both the GMDS and the DPDQ), post hoc analyses revealed that there was no difference between any of the groups in terms of maternal PDI or HAZ. See Table 6.

Table 6: Comparisons of continuous variables across GMDS and DPDQ tertile groups

	GMDS-DPDQ Groups	Mean	Standard Deviation	F
Household Asset Index	1	3.72[a]	1.31	2.31*
	2	4.69[a]	0.75	
	3	3.87	0.74	
	4	4.19	1.33	
Maternal Pitt Depression Inventory	1	16.93	8.62	0.53
	2	15.33	4.62	
	3	11.80	3.90	
	4	15.42	10.40	
Maternal Parity	1	2.48[a]	1.6	2.32*
	2	1.69	0.85	
	3	1.53[a]	0.64	
	4	1.95	1.07	
Height for age z-score	1	-1.529	1.02	1.23
	2	-0.873	0.96	
	3	-0.843	0.95	
	4	-1.004	1.04	

Means with lettered superscripts differed significantly at p<0.1 with post hoc Tukey's HSD
**p<0.1, **p<0.05*
Note:
Group 1: children who performed in the top tertile of both the GMDS and DPDQ.
Group 2: children who performed in the top tertile of the GMDS but the lowest tertile of the DPDQ
Group 3: children in the lowest tertile of the GMDS but the top tertile of the DPDQ
Group 4: children in the lowest tertile of both the GMDS and the DPDQ

Chi-square analyses revealed that there were no group differences in terms of feeding choice. With regards to maternal education, children in group 1 (children who performed in the top tertile of both the GMDS and the DPDQ) were more likely to have mothers who had completed a Standard 8 level of education (df = 3, *p= 0.032*). Children in group 2 (children who performed in the top tertile of the GMDS but the lowest tertile of the DPDQ) were more likely to have mothers who had completed matric or higher levels of education. (df = 3, *p= 0.028).* Children in group 1 (children who performed in the top tertile of both the GMDS and the DPDQ) were more likely than chance to be stunted. (df = 3, p= 0.032). See Table 7.

Table 7: Comparisons of categorical variables across GMDS and DPDQ tertile groups by Chi-squared tests

	Feeding choice		***Maternal Education***		***Stunting***	
GMDS-DPDQ Groups	***Breastfed at 6 months***	***Not Breastfed at 6 months***	***Std 8***	***Matric/ Graduate***	***HAZ <-2***	***HAZ >-2***
1	12(*13*, -0.9)	3(*2*, 0.9)	19 (*13.9*, 2,5)**	6 (*11.1*, -2.5)**	4 (*1.7*, 2.2)**	8 (*10.3*, -2.2)**
2	12(*10.4*, 1.6)	0(*1.6*, -1.6)	4(*7.2*, -2)**	9(5.*8*, 2)**	1(*1.6*, -0.6)	10 (*9.4*, 0.6)
3	4(*5.2*, -1.5)	2(*0.8*, 1.5)	8(*8.3*, -0.2)	7(*6.7*, 0.2)	1 (*1.7*, -0.7)	11 (*10.3*, 0.7)
4	11(*10.4*, 0.6)	1(*1.6*, -0.6)	10(*11.6*, -0.8)	11(*9.4*, 0.8)	1 (*2*, -0.9)	13 (*12*, 0.9)

Observed count (*Expected count*, Adjusted standardised residual)

*p<0.1, **p<0.05

4.0 Discussion

The most significant findings in this study are the associations between the neurocognitive assessments and maternal parity, maternal level of education and linear growth. While lower maternal parity and higher levels maternal education were significantly associated with higher scores on the DPDQ at 5 years of age, improved linear growth was associated with higher scores in both the 1-year GMDS and the 5-year DPDQ. The expected significant trends associated with breastfeeding at 6 months of age, household asset index, and maternal Pitt Depression Inventory were not demonstrated.

Interestingly, in terms of children's profiles of neurocognitive development between 1 and 5 years of age, children who performed in the top tertiles on both the GMDS and the DPDQ were more likely to have mothers with a Standard 8 level of education, and less likely to have mothers with matric or a graduate level of education; whereas children who performed in the top tertile of the GMDS but the lowest tertile of the DPDQ were more likely to have mothers with matric or graduate level of education than to have mothers with only a Standard 8 level of education. The other unexpected finding in analysis of these profiles is the finding that children who performed in the top tertiles of both the GMDS and DPDQ (group 1) were more likely than by chance to be stunted.

Limitations of this study

Neurocognitive assessments in any study are fraught with bias, and have limited correlation to neurophysical processes demonstrable only by neuro-imaging techniques. Neurocognitive assessments outside of high-income countries are limited by language and cultural barriers, and have very little data validating their efficacy. Neurocognitive developmental assessments in this study were performed by trained examiners using adapted assessments tools, however these were performed by multiple examiners with limited consistency which may have

introduced subjective bias. The GMDS is an assessment tool whereas DPDQ is a screening tool and would have missed children with learning disabilities. **Furthermore, as the GMDS is a formal assessment, and the DPDQ a screening tool, the DPDQ results may not be as robust as those attained from the GMDS**. As delineated earlier, neither tool has been standardised in South Africa and may falsely underestimate neurocognitive development. However as culture is less likely to play a role in neurocognitive developmental processes at 12 months of age, the GMDS may have given a more accurate reflection of the development of the child at that age. The study may have been less biased had the follow up of children's cognitive development at 5 years also been assessed using the GMDS.

In terms of the factors influencing early childhood neurocognitive development, as with any similar study, because there are innumerable factors influencing the process, it is impossible to isolate any single factor to explain a neurocognitive developmental pattern. Any observed association may be explained by either expected or unexpected confounding variables, as it is very difficult to collect data on every variable that may influence the complex process of early childhood neurocognitive development. Other possible confounding factors, which were not available in the current study, include children's Human Immunodeficiency Virus (HIV) status and psychosocial factors associated with the disease which are known to have negative cumulative influences on child neurodevelopment.

However, as there is little data in the LAMICs on patterns of and factors influencing early childhood neurocognitive development, findings from this report add to current knowledge and forms a platform for much needed further research.

Discussion of Results

Breastfeeding

Breastfeeding at 6 months was not significantly associated with higher scores on either the GMDS or DPDQ. This is inconsistent with extant literature.[16, 17, 25, 26] This may in part be explained by relative protein deficiency of breastmilk for preterm infants[61], as prematurity was not adjusted for in this analysis. This lack of association may be explained by the low number of non-breastfed infants in the study (15%), it is thus possible that the sample size was too small to detect the expected difference between the groups. The presence of breastfeeding at 6 months also did not appear to significantly alter the trajectory of the child's neurocognitive development, as there was no significant difference found in feeding choice between the four GMDS-DPDQ groups.

Linear Growth

The data suggests that higher height-for age z-score is significantly associated with the GMDS and the DPDQ, children who were stunted tended to also have lower scores on the DPDQ and a trend towards lower scores on the GMDS. This is consistent with similar studies that have found a positive association between linear growth and improved neurocognitive development.[14, 33, 34, 36] In terms of neurocognitive developmental trajectories, there were more stunted children than expected that performed consistently in the top tertiles of the GMDS and DPDQ ($p<0.05$), but neither stunting nor absolute height for age z-score differed between the other tertile groups. **This is an important finding as it highlights the multifactorial nature of neurocognitive development, suggesting that the features of the home-environment that result in stunting may be more important than stunting itself in the developing brain[33, 34, 36].** It also suggests that the association between stunting and neurocognitive development is more complex than previously reported. Casale et al [35] showed that children who recover from stunting by the age of two achieve similar neurocognitive

scores to those who were not stunted, thus suggesting some reversibility. The unexpectedly higher proportion of stunted children performing in the top tertiles of the GMDS and DPDQ may therefore be explained by later nutritional recovery, but this cannot be confirmed as height for age was not measured at 5 years of age.

Household demographic

Results from the current analysis indicated that children with higher DPDQ scores also tended to come from households with higher asset indices. ($p<0.1$). This is consistent with similar studies[7, 40, 41] Interestingly, when comparing across developmental patterns, children in group 2 (those who performed in the top tertile of the GMDS but in the lowest tertile of the DPDQ) tended to come from households with higher household asset indices than those in group 1 (those who performed consistently in the top tertiles in both the GMDS and DPDQ). The effect of poverty on the developing brain is known to be multifactorial, and is hypothesized to be in part due to reduced language and cognitive stimulation at home[38] which is expected to be greater in homes with higher household asset indices. It is difficult to explain why this association is different in this study. The findings of this study point to the need for further research to better understand the complex associations between early cognitive development and household demographics in the South African context. Future directions might include examining the mediating or moderating factors underlying the link between household demographics and early cognitive development.

Maternal level of education

Maternal education was positively associated with DPDQ scores ($p<0.001$). This effect was not seen with the GMDS. The literature suggests that higher levels of maternal education contribute to more stimulating and safer home environments that improve early childhood neurocognitive development. [44, 45] A similar study has suggested that maternal education

buffers the effect of an initially poor neurocognitive developmental assessment on a later neurocognitive assessment.[13] However, children who performed in the top tertile of both the GMDS and the DPDQ were significantly less likely to have mothers with higher levels of education. Furthermore, children who performed in the top tertile of the GMDS but the lowest tertile of the DPDQ were more likely to have mothers with higher levels of education. This unexpected lower proportion of children of highly educated mothers in group 1 and higher proportion in group 2 differs from extant literature, and more research need to be performed.

Maternal depression

There was a trend towards higher GMDS and DPDQ scores with lower maternal Pitt Depression Inventories. There was no significant difference in the maternal PDI across the 4 GMDS-DPDQ tertile groups, however, the mean depression score was lowest in group 3 (children who performed in the lowest tertile of the GMDS and the top tertile of the DPDQ). This supports the notion that maternal mental health has a significant influence on children's neurocognitive development [50, 52, 57]. Children with initial poor cognitive development during infancy, but with mothers who are emotionally healthy and hence emotionally available and attuned to their children's needs, may receive the stimulation and care necessary to improve their cognitive development[52].

Maternal parity

Results from the current study support prior research that higher maternal parity is associated with poorer neurocognitive outcomes in early childhood[44]. This study's findings show that DPDQ and parity are negatively associated. Furthermore, those children who performed in the lowest tertile of the GMDS but in the top tertile of the DPDQ (group 3) had significantly fewer siblings than those who performed consistently in the top tertiles of both assessments (group 1). This suggests that a lower maternal parity, as with good mental health,

may allow the mother the time and resources necessary to appropriately stimulate her child to improve his/her neurocognitive development.

5.0 Conclusion

This study has shown the expected positive effect of higher levels of maternal education, better linear growth and lower maternal parity on early childhood neurocognitive development in **predominantly** black South African children. It did not find the expected associations between neurocognitive development and household demographics, breastfeeding and maternal depression.

There is a paucity of research concerning early childhood neurocognitive development in low and middle income countries and especially in the South African context. Although these findings from the Birth to Twenty cohort do add to current knowledge, our findings here highlight the need for further research. The main gaps in current knowledge identified by this study include the development of a standardised neurocognitive assessment tool for South African children, the relationship between household demographics and early cognitive development, and neurocognitive development patterns in black South African children.

It is a very exciting field for future research. As neuroimaging techniques develop, researchers will be able to better understand the complex processes of early childhood neurodevelopment, and more accurately delineate how this process is influenced by genetic and environmental factors.

6.0 Recommendations

This study relied on developmental tools modified **for** the South African context. More work needs to be done on validating these tools. It will be useful to reappraise various moderating factors on early childhood development, particularly household demographics, stunting and maternal level of education.

7.0 Appendices

Appendix 1:

Human Research Ethics Committee (Medical) Clearance Certificate

R14/49 Dr Jessica Rule

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150151

NAME: (Principal Investigator)	Dr Jessica Rule
DEPARTMENT:	Paediatrics Public Health MRC/ Wits Developmental Pathways for Health Research Unit
PROJECT TITLE:	Factors Influencing Early Childhood Neurodavelopment: Evidence from the Birth to Twenty Cohort
DATE CONSIDERED:	30/01/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Celia Hsiao and Prof Lorna Jacklin
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	30/01/2015

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature

Date: 7 February 2015

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 2:

<u>Permission from the MRC/Wits Developmental Pathways for Health Research Unit</u>

MRC/Wits Developmental Pathways for Health Research Unit,
Department of Paediatrics,
School of Clinical Medicine,
Faculty of Health Sciences,
University of the Witwatersrand, Johannesburg
Tel: 011-9331122

To Whom It May Concern,

This letter serves to provide permission for Jessica Rule to have access to the necessary data from the Birth to Twenty study, based in the Developmental Pathways for Health Research Unit, required to complete her Master of Medicine research project.

Specifically the data will include the following variables:

a. The Griffiths Mental Development Scale
b. The Denver Prescreening Developmental Questionnaire
c. The mother's level of education
d. The maternal PIT depression score
e. Maternal feeding choice
f. Child stunting
g. Household asset index
h. The number of previous live births

Sincerely.

Professor Shane Norris
Director
MRC/WITS Developmental Pathways for Health Research Unit
011-933-1122
Shane.Norris@wits.ac.za

Appendix 3:

<u>Tunritin Certificate</u>

8.0 References

1. Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B, et al. Developmental potential in the first 5 years for children in developing countries. Lancet. 2007;369(9555):60-70.
2. Richter L, Norris S, Pettifor J, Yach D, Cameron N. Cohort Profile: Mandela's children: the 1990 Birth to Twenty study in South Africa. International Journal of Epidemiology. 2007;36(3):504-11.
3. Griffiths R. The abilities of young children: A comprehensive system of mental measurement for the first eight years of life. London, England1970.
4. Jacklin L, Cockroft, K. The Griffiths Mental Developmental scales: An overview and consideration of their relevance for South Africa. Psychological Assessment in South Africa: Research and applications2012. p. 169-85.
5. Luiz DM, Foxcroft CD, Stewart R. The construct validity of the Griffiths Scales of Mental Development. Child: Care, Health and Development. 2001;27(1):73-83.
6. Laughton B, Cornell M, Grove D, Kidd M, Springer PE, Dobbels E, et al. Early antiretroviral therapy improves neurodevelopmental outcomes in infants. Aids. 2012;26(13):1685-90.
7. Laughton B, Springer P, Grove D, Seedat S, Cornell M, Kidd M, et al. Longitudinal developmental profile of children from low socio-economic circumstances in Cape Town, using the 1996 Griffiths Mental Development Scales. South African Journal of Child Health. 2010;4(4):106-11.
8. Davies L, Dunn M, Chersich M, Urban M, Chetty C, Olivier L, et al. Developmental delay of infants and young children with and without fetal alcohol spectrum disorder in the Northern Cape Province, South Africa. African Journal of Psychiatry. 2011;14(4): 298-305.
9. Amod Z, Cockcroft K, Soellaart B. Use of the 1996 Griffiths Mental Development Scales for infants: a pilot study with a Black, South African sample. Journal of Child and Adolescent Mental Health. 2007;19(2):123-30.
10. Frankenburg WK, van Doorninck WJ, Liddell TN, Dick NP. The Denver prescreening developmental questionnaire (PDQ). Pediatrics. 1976;57(5):744-53.
11. Frankenburg WK, Dodds J, Archer P, Shapiro H, Bresnick B. The Denver II: a major revision and restandardization of the Denver Developmental Screening Test. Pediatrics. 1992;89(1):91-7.
12. Luiz DM, Foxcroft CD, Tukulu AN. The Denver II Scales and the Griffiths Scales of Mental Development: a correlational study. Journal of Child and Adolescent Mental Health. 2004;16(2):77-81.
13. Hsiao C, Richter, LM. Early Mental Development As a Predictor of Preschool Cognitive and Behavioral Development in South Africa The Moderating Role of Maternal Education in the Birth to Twenty Cohort. Infants & Young Children. 27: Lippincott Williams & Wilkins; 2013. p. 74-87.
14. Casale D, Desmond C, Richter L. The association between stunting and psychosocial development among preschool children: a study using the South African Birth to Twenty cohort data. Child: Care, Health and Development. 2014;40(6):900-10.
15. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality. Lancet. 2000;355(9202):451-5.
16. Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding. The Cochrane Database of Systematic Reviews. 2012;8:CD003517.
17. Sacker A, Quigley MA, Kelly YJ. Breastfeeding and developmental delay: findings from the millennium cohort study. Pediatrics. 2006;118(3):e682-9.

18. Anderson JW, Johnstone BM, Remley DT. Breast-feeding and cognitive development: a meta-analysis. The American Journal of Clinical Nutrition. 1999;70(4):525-35.
19. Der G, Batty GD, Deary IJ. Effect of breast feeding on intelligence in children: prospective study, sibling pairs analysis, and meta-analysis. British Medical Journal. 2006;333(7575):945.
20. Drane DL, Logemann JA. A critical evaluation of the evidence on the association between type of infant feeding and cognitive development. Paediatric and Perinatal Epidemiology. 2000;14(4):349-56.
21. Jacobson SW, Jacobson JL. Breastfeeding and IQ: evaluation of the socio-environmental confounders. Acta Paediatrica. 2002;91(3):258-60.
22. Jacobson SW, Jacobson JL. Breast feeding and intelligence in children. British Medical Journal. 2006;333(7575):929-30.
23. Kramer MS, Aboud F, Mironova E, Vanilovich I, Platt RW, Matush L, et al. Breastfeeding and child cognitive development: new evidence from a large randomized trial. Archives of General Psychiatry. 2008;65(5):578-84.
24. Michaelsen KF, Lauritzen L, Mortensen EL. Effects of breast-feeding on cognitive function. Advances in Experimental Medicine and Biology. 2009;639:199-215.
25. Julvez J, Guxens M, Carsin AE, Forns J, Mendez M, Turner MC, et al. A cohort study on full breastfeeding and child neuropsychological development: the role of maternal social, psychological, and nutritional factors. Developmental Medicine and Child Neurology. 2014;56(2):148-56.
26. Dee DL, Li R, Lee LC, Grummer-Strawn LM. Associations between breastfeeding practices and young children's language and motor skill development. Pediatrics. 2007;119 Suppl 1:S92-8.
27. Jedrychowski W, Perera F, Jankowski J, Butscher M, Mroz E, Flak E, et al. Effect of exclusive breastfeeding on the development of children's cognitive function in the Krakow prospective birth cohort study. European Journal of Pediatrics. 2012;171(1): 151-8.
28. Guxens M, Mendez MA, Molto-Puigmarti C, Julvez J, Garcia-Esteban R, Forns J, et al. Breastfeeding, long-chain polyunsaturated fatty acids in colostrum, and infant mental development. Pediatrics. 2011;128(4):e880-9.
29. Koo W, Tank S, Martin S, Shi R. Human milk and neurodevelopment in children with very low birth weight: a systematic review. Nutrition Journal. 2014;13:94.
30. Deoni SC, Dean DC, 3rd, Piryatinsky I, O'Muircheartaigh J, Waskiewicz N, Lehman K, et al. Breastfeeding and early white matter development: A cross-sectional study. NeuroImage. 2013;82:77-86.
31. Anderson A, Burggren A. Cognitive and neurodevelopmental benefits of extended formula-feeding in infants: re: Deoni et al. 2013. NeuroImage. 2014;100:706-9.
32. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet. 2013;382(9890):427-51.
33. Martorell R, Horta BL, Adair LS, Stein AD, Richter L, Fall CH, et al. Weight gain in the first two years of life is an important predictor of schooling outcomes in pooled analyses from five birth cohorts from low- and middle-income countries. The Journal of Nutrition. 2010;140(2):348-54.
34. Berkman DS, Lescano AG, Gilman RH, Lopez SL, Black MM. Effects of stunting, diarrhoeal disease, and parasitic infection during infancy on cognition in late childhood: a follow-up study. Lancet. 2002;359(9306):564-71.
35. Crookston BT, Penny ME, Alder SC, Dickerson TT, Merrill RM, Stanford JB, et al. Children who recover from early stunting and children who are not stunted demonstrate similar levels of cognition. The Journal of Nutrition. 2010;140(11): 1996-2001.

36. Prado EL, Abubakar AA, Abbeddou S, Jimenez EY, Some JW, Ouedraogo JB. Extending the Developmental Milestones Checklist for use in a different context in Sub-Saharan Africa. Acta Paediatrica. 2014;103(4):447-54.
37. Glewwe P, King, EM. The Impact of Early Childhood Nutritional Status on Cognitive Development: Does timing of malnutrition matter? World Bank Economic Review. 2001;15(1):81-103.
38. Filmer D, Scott K, Assessing asset indices. World Bank Policy Research Working Paper Series 4605. 2008
39. Barbarin O, Khomo N, Indicators of economic status and social capital in South African townships. Childhood, 1997; 4,193–222.
40. Ginsburg C, Griffiths PL, Richter, LM Norris, SA, Residential mobility, socioeconomic context and body mass index in a cohort of urban South African adolescents. Health Place, 2013, 100, 99-107.
41. Cook JT, Frank DA, Casey PH, Rose-Jacobs R, Black MM, Chilton M, et al. A brief indicator of household energy security: associations with food security, child health, and child development in US infants and toddlers. Pediatrics. 2008;122(4):e867-75.
42. Noble KG, Houston SM, Brito NH, Bartsch H, Kan E, Kuperman JM, et al. Family income, parental education and brain structure in children and adolescents. Nature Neuroscience. 2015;18(5):773-8.
43. World Health Organization. Millenium Development Goals 2014. Available from: http:// www.who.int/topics/millennium_development_goals/en/.
44. Koutra K, Chatzi L, Roumeliotaki T, Vassilaki M, Giannakopoulou E, Batsos C, et al. Socio-demographic determinants of infant neurodevelopment at 18 months of age: Mother-Child Cohort (Rhea Study) in Crete, Greece. Infant Behavior & Development. 2012;35(1):48-59.
45. Cockcroft K, Amod Z, Soellaart B. Level of maternal education and performance of Black, South African infants on the 1996 Griffiths Mental Development Scales. African Journal of Psychiatry. 2008;11(1):44-50.
46. Voss W, Jungmann T, Wachtendorf M, Neubauer AP. Long-term cognitive outcomes of extremely low-birth-weight infants: the influence of the maternal educational background. Acta Paediatrica. 2012;101(6):569-73.
47. Ronfani L, Vecchi Brumatti L, Mariuz M, Tognin V, Bin M, Ferluga V, et al. The Complex Interaction between Home Environment, Socioeconomic Status, Maternal IQ and Early Child Neurocognitive Development: A Multivariate Analysis of Data Collected in a Newborn Cohort Study. PloS One. 2015;10(5):e0127052.
48. Hung KJ, Tomlinson M, le Roux IM, Dewing S, Chopra M, Tsai AC. Community-based prenatal screening for postpartum depression in a South African township. International Journal of Gynaecology and Obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2014;126(1):74-7.
49. Rifkin-Graboi A, Bai J, Chen H, Hameed WB, Sim LW, Tint MT, et al. Prenatal maternal depression associates with microstructure of right amygdala in neonates at birth. Biological Psychiatry. 2013;74(11):837-44.
50. Talge NM, Neal C, Glover V, Early Stress TR, Prevention Science Network F, Neonatal Experience on C, et al. Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? Journal of Child Psychology and Psychiatry, and Allied Disciplines. 2007;48(3-4):245-61.
51. O'Connor TG, Monk C, Fitelson EM. Practitioner review: Maternal mood in pregnancy and child development--implications for child psychology and psychiatry. Journal of Child Psychology and Psychiatry, and Allied Disciplines. 2014;55(2):99-111.
52. Koutra K, Chatzi L, Bagkeris M, Vassilaki M, Bitsios P, Kogevinas M. Antenatal and postnatal maternal mental health as determinants of infant neurodevelopment at 18

months of age in a mother-child cohort (Rhea Study) in Crete, Greece. Social Psychiatry and Psychiatric Epidemiology. 2013;48(8):1335-45.
53. Surkan PJ, Kennedy CE, Hurley KM, Black MM. Maternal depression and early childhood growth in developing countries: systematic review and meta-analysis. Bulletin of the World Health Organization. 2011;89(8):608-15.
54. Prendergast AJ, Humphrey JH. The stunting syndrome in developing countries. Paediatrics and International Child Health. 2014;34(4):250-65.
55. Casale D, Desmond C, Richter L. The association between stunting and psychosocial development among preschool children: a study using the South African Birth to Twenty cohort data. Child: Care, Health and Development. 2014; 40(6):900-10.
56. Walker SP, Chang SM, Wright A, Osmond C, Grantham-McGregor SM. Early childhood stunting is associated with lower developmental levels in the subsequent generation of children. The Journal of Nutrition. 2015;145(4):823-8.
57. Verkuijl N, Richter, L., Norris, SA., Stein, A., Avan, B., Ramchandani, PG. Postnatal depressive symptoms and child psychological development at 10 years: a prospective study of longitudinal data from the South African Birth to Twenty cohort. The Lancet Psychiatry. 2014;1(6):454-60.
58. World Health Organization. Nutrition Health Topics 2010 [12 September 2015]. Available from: http://www.who.int/nutrition/topics/en/.
59. Avan B, Richter LM, Ramchandani PG, Norris SA, Stein A. Maternal postnatal depression and children's growth and behaviour during the early years of life: exploring the interaction between physical and mental health. Archives of Disease in Childhood. 2010;95(9):690-5.
60. Boyce P, Stubbs J, Todd A. The Edinburgh Postnatal Depression Scale: validation for an Australian sample. The Australian and New Zealand Journal of Psychiatry. 1993;27(3): 472-6.
61. Arslanoglu S, Moro GE, Ziegler EE, The Wapm Working Group On N. Optimization of human milk fortification for preterm infants: new concepts and recommendations. Journal of Perinatal Medicine. 2010;38(3):233-8.
62. Richter LM, Victora CG, Hallal PC, Adair LS, Bhargava SK, Fall CH, et al. Cohort profile: the consortium of health-orientated research in transitioning societies. International Journal of Epidemiology. 2012;41(3):621-6.