Title: The impact of maternal nutrition on birth weight and brain development in children from low- and middle-income countries

Short Running Title: Maternal nutrition, birth weight, and brain development

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Abstract

Maternal nutrition is a key factor influencing optimal birth and child developmental outcomes. Although this is recognized globally, it is particularly relevant to low- and middle-income countries (LMICs) where the risk of malnutrition during pregnancy is high, and low birth weight (LBW) is prevalent. LBW has consistently been associated with poor health, stunted growth, and adverse neurocognitive outcomes. Less is known about the impact of maternal nutrition and LBW on neurodevelopment due to the limited focus of neuroimaging research on maternal obesity and pre-term birth in high-income countries. Maternal nutrition may be pivotal to understanding how LBW impacts the child brain in LMICs where there is a high risk of food insecurity and approximately 43% of children under the age of 5 are at risk of not reaching their developmental potential. Furthermore, examining the outcomes of LBW in babies who are small-for-gestational age (SGA) due to intrauterine growth restriction (IUGR) in LMICs is less-explored, yet important. Therefore, further neuroimaging research is needed to investigate the complex relationship between maternal nutrition, LBW and structural brain outcomes. This should be recognized as a research priority to inform nutritional interventions during pregnancy, and to optimize the developmental potential of children from LMICs.

Keywords: Birth Outcomes, Brain Development, Low Birth Weight, Maternal Nutrition, Neuroimaging

Key Notes

- The prevalence of malnutrition during pregnancy and low birth weight (LBW) is high in low-and middle-income-countries (LMICs).
- Current neuroimaging research on maternal nutrition and birth weight focuses on health priorities such as maternal obesity and pre-term birth in high-income countries.
- Given the high risk of food insecurity in LMICs, neuroimaging research is needed to explore the complex relationship between maternal nutrition, LBW, and child brain outcomes.

Introduction

Child development is influenced by multiple risk and protective factors, both antenatally and postnatally (1). Nutrition is recognized as one of the most important of these factors, being significantly associated with poor developmental outcomes (2, 3). There is a critical window in which the developing brain is rapidly changing and is extremely sensitive to environmental influences (3). During pregnancy and early postnatal life, maternal and child nutrition are key environmental factors that may be targeted to promote optimal neurodevelopment across the lifespan (4). Although this relationship is globally relevant, it is particularly important within the context of high-risk populations in low-and middle-income countries where the risk of malnutrition during pregnancy is high and many babies are born with low birth weight (LBW; 5). In this article, we review evidence on and present a conceptual framework for the complex relationship between maternal nutrition, LBW, and child brain outcomes. Furthermore, we highlight research gaps in LMIC settings that need to be addressed in order to advance our understanding of risk factors for child brain development and to inform interventions for optimized child developmental outcomes.

Nutrition and Neurodevelopment

The human brain undergoes substantial growth and maturation within the first 1000 days, from conception to two years of life (1, 3, 6). Given the rate of neurodevelopment during this time, the metabolic demand of the brain is exceptionally high, making it particularly vulnerable to nutritional deficits (4). Nutrients that support energy, carbohydrate, protein and fat metabolism are essential for optimal brain growth and neurodevelopment (3). While some nutrients may have a more global effect (e.g. protein, energy) on the developing brain, the role of other micronutrients (including iron) may have a more regional impact (7). This forms the basis of the Regionalization Hypothesis, which emphasizes the role of timing, dose, and duration of environmental influences such as nutrition due to the nonhomogeneous nature of regional brain development (3). Malnourishment and nutrient deficiencies have consistently been associated with adverse long-term cognitive and

developmental outcomes, both of which have negative repercussions at an individual and societal level (3, 5, 8).

While both the pre- and post-natal period of early life represent an important period of growth and sensitivity, there is growing recognition of the foetal origins for brain health with renewed focus on optimizing antenatal maternal well-being for improved developmental outcomes in children (1). Current intervention research provides some evidence for the importance of considering prenatal timing and prevention strategies. Some nutritional interventions including food supplementation in infancy and early childhood have been found to improve growth (9-11) and cognitive development (12). However, a growing number of studies suggest that intervention during pregnancy is needed. For example, research from the Sanitation Hygiene Infant Nutrition Efficacy (SHINE) trial in Zimbabwe has suggested that nutritional interventions administered in infancy (6-18 months) failed to improve developmental outcomes in this context, and earlier, more targeted interventions may be preferable (13). Other research (14, 15) including a meta-analysis (16) has reported that, overall, post-natal micronutrient supplementation for children in LMICs does not appear effective in promoting early cognitive outcomes. Comprehensive systematic reviews focusing specifically on post-natal iron supplementation report similar findings (17, 18).

In contrast, systematic reviews on prenatal maternal nutrition have consistently found that both balanced protein-energy supplementation (19) and micronutrient supplementation (20) during pregnancy are effective interventions to prevent stillbirth, maternal and neonatal mortality, and poor birth outcomes in undernourished mothers. Similarly, specific micronutrient interventions such as prenatal iron/folic acid supplementation have been found to improve motor and intellectual functioning in school-age children (21). This supports conclusions from a review of nutritional influences indicating that postnatal nutritional success may be dependent on foetal nutritional status (6, 22). However, there is limited research on pre-natal nutritional interventions and neurodevelopmental outcomes, with findings being inconclusive. Therefore, further research is needed in order to inform interventions aimed at improving child development.

Maternal Nutrition and Birth Outcomes

Maternal nutrition before and during pregnancy is recognized as being a vital component of antenatal care to optimize birth outcomes (23, 24). The nutrients available for the growing foetus during pregnancy are dependent on the mother's nutrient store as well as her dietary intake (25). Therefore, pre-pregnancy Body Mass Index (BMI), weight loss and gain during pregnancy, and dietary intake before and during pregnancy may all serve as potential indicators of maternal nutritional status (5, 26).

Maternal obesity or overweight during pregnancy has been linked to obstetric complications and adverse birth outcomes including gestational diabetes, pre-eclampsia, caesarian delivery, pre-term birth, large for gestational age (LGA) births, and admission to the neonatal intensive care unit (27). Furthermore, maternal obesity has been associated with adverse long-term child health outcomes including obesity in childhood and adolescence, increased cardiometabolic risk, respiratory difficulties, and poor neurodevelopmental outcomes (28, 29). This contributes to an intergenerational cycle of obesity and chronic disease (29). Obesity is recognized as a health concern particularly relevant to high-income countries (30, 31), however, the number of children who are overweight or obese is now also increasing in Africa and Asia (32). In these regions, many countries are now facing what is termed a "double burden" with an obesity pandemic co-existing alongside continued underweight and malnutrition (33).

Poor maternal nutrition and malnutrition in pregnancy has also consistently been linked to adverse birth outcomes with the most well-known being pre-term birth, LBW, and intra-uterine growth restriction (IUGR; 34). The impact of maternal malnutrition on infant birth weight is well-documented, and is recognized as a global health concern by the World Health Organization (35). A number of systematic reviews and meta-analyses have concluded that both low maternal weight during pregnancy (36) and maternal anaemia (37, 38) increase the risk of LBW in infants. This is particularly evident in LMICs such as India (26) and Nigeria (39) where undernourishment (indicated by low BMI or reduced weight gain in pregnancy, respectively) and low haemoglobin levels in pregnancy have been significantly

associated with LBW. In turn, LBW is associated with numerous health risks in childhood, including wasting and stunting (40).

In LMICs, malnutrition during pregnancy is highly prevalent, being recognized as a major risk for adverse birth outcomes such as LBW and poor childhood growth. Given that LBW has been recognized by the WHO as a global nutrition priority (35, 41), particularly in LMICs where prevalence is highest, research on the impact of maternal nutrition on the developing child brain in the LMIC context should be prioritized. This is important to minimize the risk of developmental inequalities in child (5).

Low Birth Weight Classifications

LBW describes babies who are born weighing less than 2500g with very low (VLBW) and extremely low birth weight (ELBW) recognized as being under 1500g and 1000g, respectively (42-45). LBW includes babies that are pre-term (<37 weeks) as well as those with intrauterine growth restriction (IUGR; 45). Babies that are small for gestational age (SGA) fall under the 10th percentile of birthweight for their gestational age, according to the gender specific reference for their population (46, 47). Birth weight can be delineated according to pre-term birth, IUGR, SGA and their overlap. Babies born at term or pre-term may have LBW (<2500g) that is appropriate for gestational age (AGA) or SGA (below 10th percentile) which may be used as a proxy for IUGR be due to maternal or environmental factors (48, 49).

These classifications of LBW are associated with differing etiologies, patterns of growth and morbidity, and developmental risks (45). For example, while pre-term babies born at a weight AGA tend to catch up, SGA babies born with LBW due to IUGR fail to thrive and suffer more long-term health consequences (50). IUGR has various possible causes categorized under placental and cord abnormalities (e.g. placental insufficiency), foetal factors (e.g. congenital infections and diseases), and maternal factors (e.g. age, health, substance use; 49). Of the maternal factors, poor maternal nutrition is recognized as a major determinant (5, 26, 51), especially in babies who are born at term but are SGA (48, 49, 52). While maternal pre-pregnancy BMI and weight gain during pregnancy may predict birth

weight, an adequate dietary intake (balanced energy-protein; sufficient micronutrients) reduces the risk of infants being born SGA (5). This is key given that, in poorly resourced LMIC settings, malnutrition is identified as the leading cause of LBW due to IUGR (48, 51, 53). The relationship between these intertwined categories of LBW born at term and pre-term is represented below in Figure 1.

Figure 1. Causes of IUGR and Overlapping Manifestations of Low Birth Weight (<2500g) in Babies Born at Term and Pre-Term.

We constructed this diagram to visually represent the various categories of LBW in babies born at term and pre-term (42-45). The potential underlying etiologies of IUGR are also presented to clarify the potential link between antenatal maternal nutrition and LBW in babies born at term (48, 49, 51).

Overall, LBW has been linked to adverse short and long-term infant health outcomes including increased risk of infant mortality, diminished physical growth, and a weakened immune response (52). Recent research has identified LBW as a major determinant of stunting in children (54, 55) and systematic reviews have suggested that LBW increases the risk of chronic and non-communicable diseases (56, 57). In addition to increasing the burden on the health systems in LMICs, systematic reviews have further shown that LBW is associated with poor cognitive outcomes in childhood (58-60) as well as adulthood (61). Even children with marginally LBW have been found to have more cognitive difficulties than children with a normal birth weight (62). However, understanding the causal pathways which link maternal nutrition, LBW and poor infant neurodevelopmental outcomes is complex, and further research is needed.

Nutrition and Neuroimaging Research

The advent of neuroimaging has provided researchers with non-invasive tools to directly examine the effect of maternal nutrition on brain structure and function (Isaacs, 2013). Given the link between brain structure and neurocognitive outcomes (63, 64), this provides an opportunity to further understand how maternal nutrition and LBW may influence later infant outcomes. It is recognized that the prevalence of food insecurity, malnutrition and LBW is higher in LMICs (35), yet most neuroimaging research thus far has been done in high-income countries (65). This may in part be due to the high costs of MRI technology, making it an inaccessible technology for many LMICs and resulting in disproportionately fewer neuroimaging research studies emerging from these regions of the world (66).

Research from high-income countries has mainly focused on maternal BMI within the context of obesity, or maternal dietary intake during pregnancy in terms of specific micronutrients. Neuroimaging research from the United States has found that higher maternal BMI during pregnancy is associated with changes in hemispheric connectivity (67), altered white matter development (68), and changes in resting state connectivity in the infant brain (69). Similarly, neuroimaging research on maternal dietary intake from North America and the United Kingdom has identified omega-3 fatty acids and iron to be associated with

increased regional brain volumes (70, 71) and higher fractional anisotropy values in the neonatal cortical grey matter (72), respectively. Therefore, while there is evidence to suggest a neural sensitivity of the child brain to alterations in maternal nutritional status, the existing research available is limited. While maternal iron-deficient anaemia has been associated with reduced hippocampal volume in India (73), very little neuroimaging research has examined the direct relationship between maternal nutritional status (maternal anthropometry and nutritional status) and child brain outcomes within a LMIC context of food insecurity and poor nutrition.

Separately, some studies have examined links between birth weight and brain outcomes, mainly in the context of prematurity. According to a recent systematic review (58), neuroimaging studies have reported a strong relationship between very low birth weight (VLBW; <1500g), cognitive outcomes (in childhood and adulthood), and structural brain abnormalities such as reduced cortical surface area, ventricular dilation, regional cortical thinning, white matter changes, and reduced overall brain volume. In terms of regional brain volume alterations in the context of VLBW, various structures have been implicated including the cerebral white matter, subcortical grey matter, cerebellum, brain stem, thalamus, corpus callosum (74-76) and, particularly, the hippocampus (77, 78). In a study comparing pre-term children born with weight AGA with preterm infants with weight SGA due to IUGR, the thalamus and basal ganglia volumes were found to be significantly reduced in the latter at 36 weeks (adjusted age; 79).

Overall, current neuroimaging research on LBW is limited given that it has mostly been conducted in high-income countries and has focused on pre-term birth (<37 weeks). In one systematic review only 3 of the 43 research countries were from LMICs (Taiwan, Brazil and India; 58). This makes current neuroimaging research less relevant to LMICs, where many LBW births are SGA due to IUGR (45, 48). These are often linked with poor maternal health and nutrition (5, 50). Given the differing causal factors, trajectories, and risks associated with these birth weight classifications (pre-term versus term; AGA versus SGA

due to IUGR), neuroimaging research regarding their unique predictive impact on brain development is important.

Prioritizing neuroimaging research on birth weight and pre-term birth in high-income countries has also led to an emphasis being placed on VLBW (<1500g). Therefore, very little is known about the neurodevelopmental impact of other birth weight classifications such as LBW (<2500g), or birth weight within the normal range but at varying ends of the spectrum. While it is understood that very small babies are at high risk of brain abnormalities, the risk associated with less severe presentations of LBW is poorly documented. Similarly, the protective effects of higher birth weight on brain outcomes are unknown, despite the relevance of such information for intervention work.

Furthermore, the specific role of maternal nutrition may be pivotal to fully understanding how birth weight impacts the child brain (5, 35, 80). While poor maternal nutrition is a common cause of LBW in babies born at term, there are various other etiologies including multiple pregnancies, maternal infection, smoking and alcohol use, and chronic conditions such as diabetes and high blood pressure (26, 45, 51). Therefore, further neuroimaging research controlling for covariates is required to determine the nature of the relationship between maternal nutrition (as indicated by maternal anthropometry and nutritional status during pregnancy), LBW, and child brain development. A conceptual framework model is presented in Figure 2.

Figure 2. The Conceptual Relationship Between Food Insecurity, Maternal Nutrition, Birth Outcomes and Child Development in the LMIC Context

This conceptual framework demonstrates how food insecurity (26, 51, 81) may predict poor maternal nutrition in LMICs. In turn, poor maternal nutrition is one of several important determinants of adverse birth outcomes (19, 34) such as LBW (26, 51). Based on previous literature (58), we hypothesize that LBW will predict altered brain development and, consequently, poor neurodevelopmental outcomes (63). Poor birth and developmental outcomes may contribute to an intergenerational feedback loop (5).

A focus on the LMIC Context

Although the role of nutrition in child development is recognized on a global scale, this relationship is particularly relevant to populations in LMICs (5, 8). Over 250 million children in LMICs are at risk of not reaching their developmental potential (82). While multiple risk factors have been recognized as contributors, nutrition plays a key role in sub-Saharan Africa (2, 83). According to the 'State of Food Security and Nutrition in the World' report (80), Africa has the highest prevalence of undernourishment in the world, and accounts for 36.4% of the global total. In turn, poor maternal and child nutrition associated with poverty in LMICs puts children at increased risk of developmental inequalities (5).

Globally, 15-20% of babies are born with LBW and infants in LMICs are most vulnerable, despite having the highest likelihood of under-reporting (35). Maternal undernourishment characterized by low BMI is evident in 10-19% of pregnant mothers in LMICs, significantly increasing the risk of LBW (16% in LMICs) in children (5). In sub-Saharan Africa alone, it is estimated that 13% of babies are born with LBW (35). Furthermore, in 2010, it was estimated that 32.4 million (27%) neonates in LMICs were born SGA (<10th percentile), of whom 29.7 million were born at term (≥ 37) and 10.6 million were born at term with LBW (<2500g; 45). This emphasizes the prevalence of LBW due to IUGR in the LMIC context.

LMICs continue to represent the most vulnerable populations with food insecurity and nutritional status deteriorating further due to the impact of COVID-19 on health and socio-economic status (80). In a South African birth cohort study, both tangible resources (income, social assistance and HIV status) and mental resources (maternal depression and trauma exposure, maternal education) predicted perceived food insecurity (81). Given that these predictive factors are highly prevalent in LMICs, neuroimaging research on nutrition in this context is key to optimizing child health and development.

Conclusion

Poor maternal nutrition is associated with adverse birth outcomes, including LBW. In turn, LBW has consistently been linked to poor health and adverse neurocognitive outcomes in childhood and in later life. Furthermore, LBW may create inequalities in early childhood that perpetuate the cycle of poverty in LMICs (5) with downstream effects on human capital (i.e. school achievement, economic productivity) later in life (56, 57). MRI studies in high-income countries have shown associations between prematurity, birthweight, and brain structural outcomes. However, there is a significant lack of neuroimaging research on the relationship between maternal nutrition, birth weight, and brain outcomes in LMICs despite the increased prevalence of LBW, and the high risk of food insecurity and malnutrition in this context. Additionally, there is limited insight into the brain outcomes associated with varied presentations of birth weight in children, resulting in failure to distinguish the unique impact of LBW due to IUGR in SGA babies born at term. Neuroimaging research exploring the complex relationship between maternal nutritional status, LBW, and child brain development in an LMIC context, where there is a high prevalence of poor maternal nutrition and food insecurity, is needed. This will increase our understanding of risk factor pathways and may inform nutritional interventions to optimize the developmental potential of children in high-risk settings.

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JER is the first author of this paper which was conducted in affiliation with the University of Cape Town. The conceptualization, literature review, figures and write-up were conducted by JER with input from KAD and CJW. JER drafted the review article with guidance and critical review from KAD and CJW. KAD and CJW revised the manuscript critically for intellectual content. All authors reviewed and approved the final manuscript.

Complete List of Abbreviations

LMIC: Low-and-Middle-Income Country

HBW: High Birth Weight

LBW: Low Birth Weight

VLBW: Very Low Birth Weight

ELBW: Extremely Low Birth Weight

SGA: Small for Gestational Age

AGA: Appropriate for Gestational Age

IUGR: Intrauterine Growth Restriction

BMI: Body Mass Index

MRI: Magnetic Resonance Imaging

WHO: World Health Organization

Statements of Conflict of Interest

The authors have no relevant financial or non-financial conflicts of interest to disclose. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the content of this manuscript. The authors have no financial or proprietary interests in any material discussed in this article.

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References

1. Donald KA, Wedderburn CJ, Barnett W, Nhapi RT, Rehman AM, Stadler JA, et al. Risk and protective factors for child development: An observational South African birth cohort. *PLoS medicine* 2019; 16 9:e1002920.
2. Ford ND, Stein AD. Risk factors affecting child cognitive development: A summary of nutrition, environment, and maternal-child interaction indicators for sub-Saharan Africa. *Journal of developmental origins of health and disease* 2016; 7 2:197.
3. Georgieff MK, Ramel SE, Cusick SE. Nutritional influences on brain development. *Acta Paediatrica* 2018; 107 8:1310-21.
4. Isaacs EB. Neuroimaging, a new tool for investigating the effects of early diet on cognitive and brain development. *Frontiers in human neuroscience* 2013; 7:445.
5. 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.
6. Cusick SE, Georgieff MK. The role of nutrition in brain development: the golden opportunity of the “first 1000 days”. *The Journal of pediatrics* 2016; 175:16-21.
7. Georgieff MK. Nutrition and the developing brain: nutrient priorities and measurement. *The American journal of clinical nutrition* 2007; 85 2:614S-20S.
8. 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.
9. Kristjansson E, Francis DK, Liberato S, Jandu MB, Welch V, Batal M, et al. Food supplementation for improving the physical and psychosocial health of socio-economically disadvantaged children aged three months to five years: a systematic review. *Campbell Systematic Reviews* 2015; 11 1:1-226.
10. Lassi ZS, Rind F, Irfan O, Hadi R, Das JK, Bhutta ZA. Impact of infant and young child feeding (IYCF) nutrition interventions on breastfeeding practices, growth and

- mortality in low-and middle-income countries: systematic review. *Nutrients* 2020; 12 3:722.
11. Das JK, Salam RA, Saeed M, Kazmi FA, Bhutta ZA. Effectiveness of interventions for managing acute malnutrition in children under five years of age in low-income and middle-income countries: A systematic review and meta-analysis. *Nutrients* 2020; 12 1:116.
 12. Ip P, Ho FKW, Rao N, Sun J, Young ME, Chow CB, et al. Impact of nutritional supplements on cognitive development of children in developing countries: A meta-analysis. *Scientific reports* 2017; 7 1:1-9.
 13. Gladstone MJ, Chandna J, Kandawasvika G, Ntozini R, Majo FD, Tavengwa NV, et al. Independent and combined effects of improved water, sanitation, and hygiene (WASH) and improved complementary feeding on early neurodevelopment among children born to HIV-negative mothers in rural Zimbabwe: substudy of a cluster-randomized trial. *PLoS medicine* 2019; 16 3:e1002766.
 14. Murray-Kolb LE, Khatry SK, Katz J, Schaefer BA, Cole PM, LeClerq SC, et al. Preschool micronutrient supplementation effects on intellectual and motor function in school-aged Nepalese children. *Archives of pediatrics & adolescent medicine* 2012; 166 5:404-10.
 15. Pongcharoen T, DiGirolamo AM, Ramakrishnan U, Winichagoon P, Flores R, Martorell R. Long-term effects of iron and zinc supplementation during infancy on cognitive function at 9 y of age in northeast Thai children: a follow-up study-. *The American journal of clinical nutrition* 2011; 93 3:636-43.
 16. Larson LM, Yousafzai AK. A meta-analysis of nutrition interventions on mental development of children under-two in low-and middle-income countries. *Maternal & child nutrition* 2017; 13 1:e12229.
 17. Pasricha S-R, Hayes E, Kalumba K, Biggs B-A. Effect of daily iron supplementation on health in children aged 4–23 months: a systematic review and meta-analysis of randomised controlled trials. *The Lancet Global Health* 2013; 1 2:e77-e86.

18. Wang B, Zhan S, Gong T, Lee L. Iron therapy for improving psychomotor development and cognitive function in children under the age of three with iron deficiency anaemia. *Cochrane Database of Systematic Reviews* 2013; 6.
19. Imdad A, Bhutta ZA. Maternal nutrition and birth outcomes: Effect of balanced protein-energy supplementation. *Paediatric and perinatal epidemiology* 2012; 26:178-90.
20. Ramakrishnan U, Grant F, Goldenberg T, Zongrone A, Martorell R. Effect of women's nutrition before and during early pregnancy on maternal and infant outcomes: a systematic review. *Paediatric and perinatal epidemiology* 2012; 26:285-301.
21. Christian P, Murray-Kolb LE, Khatry SK, Katz J, Schaefer BA, Cole PM, et al. Prenatal micronutrient supplementation and intellectual and motor function in early school-aged children in Nepal. *Jama* 2010; 304 24:2716-23.
22. Wachs TD, Georgieff M, Cusick S, McEwen BS. Issues in the timing of integrated early interventions: contributions from nutrition, neuroscience, and psychological research. 2015.
23. WHO. WHO recommendations on antenatal care for a positive pregnancy experience: *World Health Organization*, 2016.
24. Black RE, Allen LH, Bhutta ZA, Caulfield LE, De Onis M, Ezzati M, et al. Maternal and child undernutrition: global and regional exposures and health consequences. *The lancet* 2008; 371 9608:243-60.
25. Nnam N. Improving maternal nutrition for better pregnancy outcomes. *Proceedings of the Nutrition Society* 2015; 74 4:454-9.
26. Sharma M, Mishra S. Effects of maternal health and nutrition on birth weight of infant. *International Journal of Science and Research* 2014; 3 6:855-8.
27. Yang Z, Phung H, Freebairn L, Sexton R, Raulli A, Kelly P. Contribution of maternal overweight and obesity to the occurrence of adverse pregnancy outcomes. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2019; 59 3:367-74.

28. Reynolds RM. Childhood obesity: the impact of maternal obesity on childhood obesity. *Maternal obesity and pregnancy*: Springer, 2012.
29. Baptiste-Roberts K. Maternal obesity and implications for the long-term health of the offspring. *Obesity during pregnancy in clinical practice*: Springer, 2014.
30. De Onis M, Blössner M. Prevalence and trends of overweight among preschool children in developing countries. *The American journal of clinical nutrition* 2000; 72 4:1032-9.
31. Collaborators GO. Health effects of overweight and obesity in 195 countries over 25 years. *New England Journal of Medicine* 2017; 377 1:13-27.
32. De Onis M, Blössner M, Borghi E. Global prevalence and trends of overweight and obesity among preschool children. *The American journal of clinical nutrition* 2010; 92 5:1257-64.
33. WHO. Global nutrition targets 2025: childhood overweight policy brief. World Health Organization; 2014
34. Abu-Saad K, Fraser D. Maternal nutrition and birth outcomes. *Epidemiologic reviews* 2010; 32 1:5-25.
35. WHO. Global Nutrition Targets 2025: Low birth weight policy brief. World Health Organization; 2014
36. Han Z, Mulla S, Beyene J, Liao G, McDonald SD. Maternal underweight and the risk of preterm birth and low birth weight: a systematic review and meta-analyses. *International journal of epidemiology* 2011; 40 1:65-101.
37. Figueiredo AC, Gomes-Filho IS, Silva RB, Pereira PP, Da Mata FA, Lyrio AO, et al. Maternal anemia and low birth weight: a systematic review and meta-analysis. *Nutrients* 2018; 10 5:601.
38. Rahmati S, Delpishe A, Azami M, Ahmadi MRH, Sayehmiri K. Maternal Anemia during pregnancy and infant low birth weight: A systematic review and Meta-analysis. *International journal of reproductive biomedicine* 2017; 15 3:125.
39. Amosu A, Degun A. Impact of maternal nutrition on birth weight of babies. 2014.

40. Blankenship JL, Cashin J, Nguyen TT, Ip H. Childhood stunting and wasting in Myanmar: Key drivers and implications for policies and programmes. *Maternal & Child Nutrition* 2020; 16:e12710.
41. WHO. Global nutrition targets 2025: Policy brief series. World Health Organization; 2014
42. Kramer MS. Intrauterine growth and gestational duration determinants. *Pediatrics* 1987; 80 4:502-11.
43. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. *Bulletin of the world health organization* 1987; 65 5:663.
44. Villar J, Belizán J. The relative contribution of prematurity and fetal growth retardation to low birth weight in developing and developed societies. *American journal of obstetrics and gynecology* 1982; 143 7:793-8.
45. Lee AC, Katz J, Blencowe H, Cousens S, Kozuki N, Vogel JP, et al. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. *The Lancet Global Health* 2013; 1 1:e26-e36.
46. WHO. Physical status: The use of and interpretation of anthropometry, Report of a WHO Expert Committee: *World Health Organization*, 1995.
47. De Onis M, Habicht J-P. Anthropometric reference data for international use: recommendations from a World Health Organization Expert Committee. *The American journal of clinical nutrition* 1996; 64 4:650-8.
48. De Onis M, Blössner M, Villar J. Levels and patterns of intrauterine growth retardation in developing countries. *European journal of clinical nutrition* 1998; 52:S5-15.
49. Fleiss B, Wong F, Brownfoot F, Shearer IK, Baud O, Walker DW, et al. Knowledge gaps and emerging research areas in intrauterine growth restriction-associated brain injury. *Frontiers in endocrinology* 2019; 10:188.

50. Barros FC, Huttly S, Victora C, Kirkwood BR, Vaughan JP. Comparison of the causes and consequences of prematurity and intrauterine growth retardation: a longitudinal study in southern Brazil. *Pediatrics* 1992; 90 2:238-44.
51. Mumbare SS, Maindarkar G, Darade R, Yenge S, Tolani MK, Patole K. Maternal risk factors associated with term low birth weight neonates: a matched-pair case control study. *Indian pediatrics* 2012; 49 1:25-8.
52. Martorell R, González-Cossío T. Maternal nutrition and birth weight. *American Journal of Physical Anthropology* 1987; 30 S8:195-220.
53. Mavalankar D, Gray R, Trivedi C, Parikh V. Risk factors for small for gestational age births in Ahmedabad, India. *Journal of tropical pediatrics* 1994; 40 5:285-90.
54. Utami NH, Rachmalina R, Irawati A, Sari K, Rosha BC, Amaliah N. Short birth length, low birth weight and maternal short stature are dominant risks of stunting among children aged 0-23 months: evidence from Bogor Longitudinal Study on Child Growth and Development, Indonesia. *Malaysian Journal of Nutrition* 2018; 24 1.
55. Aryastami NK, Shankar A, Kusumawardani N, Besral B, Jahari AB, Achadi E. Low birth weight was the most dominant predictor associated with stunting among children aged 12–23 months in Indonesia. *BMC Nutrition* 2017; 3 1:1-6.
56. Risnes KR, Vatten LJ, Baker JL, Jameson K, Sovio U, Kajantie E, et al. Birthweight and mortality in adulthood: a systematic review and meta-analysis. *International journal of epidemiology* 2011; 40 3:647-61.
57. Victora CG, Adair L, Fall C, Hallal PC, Martorell R, Richter L, et al. Maternal and child undernutrition: consequences for adult health and human capital. *The lancet* 2008; 371 9609:340-57.
58. Farajdokht F, Sadigh-Eteghad S, Dehghani R, Mohaddes G, Abedi L, Bughchechi R, et al. Very low birth weight is associated with brain structure abnormalities and cognitive function impairments: A systematic review. *Brain and cognition* 2017; 118:80-9.

59. Shenkin SD, Starr JM, Deary IJ. Birth weight and cognitive ability in childhood: a systematic review. *Psychological bulletin* 2004; 130 6:989.
60. Gu H, Wang L, Liu L, Luo X, Wang J, Hou F, et al. A gradient relationship between low birth weight and IQ: A meta-analysis. *Scientific reports* 2017; 7 1:1-13.
61. Grove BJ, Lim SJ, Gale CR, Shenkin SD. Birth weight and cognitive ability in adulthood: A systematic review and meta-analysis. *Intelligence* 2017; 61:146-58.
62. Starnberg J, Norman M, Westrup B, Domellöf M, Berglund SK. Lower cognitive test scores at age 7 in children born with marginally low birth weight. *Pediatric research* 2018; 83 6:1129-35.
63. Wedderburn CJ, Subramoney S, Yeung S, Fouche J-P, Joshi SH, Narr KL, et al. Neuroimaging young children and associations with neurocognitive development in a South African birth cohort study. *NeuroImage* 2020:116846.
64. Gilmore JH, Knickmeyer RC, Gao W. Imaging structural and functional brain development in early childhood. *Nature Reviews Neuroscience* 2018; 19 3:123.
65. Galler JR, Bringas-Vega ML, Tang Q, Rabinowitz AG, Musa KI, Chai WJ, et al. Neurodevelopmental effects of childhood malnutrition: A neuroimaging perspective. *NeuroImage* 2021; 231:117828.
66. Azhari A, Truzzi A, Neoh MJ-Y, Balagtas JPM, Tan HH, Goh PP, et al. A decade of infant neuroimaging research: What have we learned and where are we going? *Infant Behavior and Development* 2020; 58:101389.
67. Norr ME, Hect JL, Lenniger CJ, Van den Heuvel M, Thomason ME. An examination of maternal prenatal BMI and human fetal brain development. *Journal of Child Psychology and Psychiatry* 2020.
68. Ou X, Thakali KM, Shankar K, Andres A, Badger TM. Maternal adiposity negatively influences infant brain white matter development. *Obesity* 2015; 23 5:1047-54.
69. Li X, Andres A, Shankar K, Pivik R, Glasier C, Ramakrishnaiah R, et al. Differences in brain functional connectivity at resting state in neonates born to healthy obese or normal-weight mothers. *International Journal of Obesity* 2016; 40 12:1931-4.

70. Morton SU, Vyas R, Gagoski B, Vu C, Litt J, Larsen RJ, et al. Maternal dietary intake of omega-3 fatty acids correlates positively with regional brain volumes in 1-month-old term infants. *Cerebral Cortex* 2020; 30 4:2057-69.
71. Ogundipe E, Tusor N, Wang Y, Johnson M, Edwards A, Crawford M. Randomized controlled trial of brain specific fatty acid supplementation in pregnant women increases brain volumes on MRI scans of their newborn infants. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 2018; 138:6-13.
72. Monk C, Georgieff MK, Xu D, Hao X, Bansal R, Gustafsson H, et al. Maternal prenatal iron status and tissue organization in the neonatal brain. *Pediatric research* 2016; 79 3:482-8.
73. Basu S, Kumar D, Anupurba S, Verma A, Kumar A. Effect of maternal iron deficiency anemia on fetal neural development. *Journal of Perinatology* 2018; 38 3:233-9.
74. Abernethy LJ, Palaniappan M, Cooke RW. Quantitative magnetic resonance imaging of the brain in survivors of very low birth weight. *Archives of disease in childhood* 2002; 87 4:279-83.
75. Bjuland KJ, Rimol LM, Løhaugen GC, Skranes J. Brain volumes and cognitive function in very-low-birth-weight (VLBW) young adults. *European Journal of Paediatric Neurology* 2014; 18 5:578-90.
76. Taylor HG, Filipek PA, Juranek J, Bangert B, Minich N, Hack M. Brain volumes in adolescents with very low birth weight: effects on brain structure and associations with neuropsychological outcomes. *Developmental neuropsychology* 2011; 36 1:96-117.
77. Aanes S, Bjuland KJ, Skranes J, Løhaugen GC. Memory function and hippocampal volumes in preterm born very-low-birth-weight (VLBW) young adults. *NeuroImage* 2015; 105:76-83.
78. Aanes S, Bjuland KJ, Winsnes Lærum A, Wieder S, Evensen KAI, Indredavik M, et al. Relationship between hippocampal subfield volumes and memory function in

- adults born preterm with very low birth weight (VLBW). *Clin Obstet Gynecol Reprod Med* 2020; 6:1-11.
79. Bruno CJ, Bengani S, Gomes WA, Brewer M, Vega M, Xie X, et al. MRI differences associated with intrauterine growth restriction in preterm infants. *Neonatology* 2017; 111 4:317-23.
80. FAO I, UNICEF, WHO. The State of Food Security and Nutrition in the World. Transforming food systems for affordable healthy diets. Rome, FAO: Food and Agriculture Organisation of the United Nations; 2020
81. Pellowski JA, Barnett W, Kuo CC, Koen N, Zar HJ, Stein DJ. Investigating tangible and mental resources as predictors of perceived household food insecurity during pregnancy among women in a South African birth cohort study. *Social Science & Medicine* 2017; 187:76-84.
82. Black MM, Walker SP, Fernald LC, Andersen CT, DiGirolamo AM, Lu C, et al. Advancing Early Childhood Development: From Science to Scale 1: Early childhood development coming of age: Science through the life course. *Lancet (London, England)* 2017; 389 10064:77.
83. Grobler WC. Perceptions of poverty: a study of food secure and food insecure households in an urban area in South Africa. *Procedia Economics and Finance* 2016; 35:224-31.