UNIVERSITI PUTRA MALAYSIA

EARLY LIFE FACTORS ASSOCIATED WITH GROWTH AND COGNITIVE DEVELOPMENT OF INFANTS AT 24 MONTHS IN SEREMBAN, MALAYSIA

NURLIYANA BINTI ABDUL RAZAK

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By

NURLIYANA BINTI ABDUL RAZAK

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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May 2021

Chair : Zalilah Mohd Shariff, PhD
Faculty : Medicine and Health Sciences

The first 2 years of life is an important period for growth and development. Exposure to adverse environment may have long-term effects on health and cognitive performance. This cohort study aimed to determine the association between early life factors with growth and cognitive development of infants at 24 months of age. A total of 117 mother-infant pairs were followed-up from 6 to 24 months. Socio-demographic background (parents' age, ethnicity, educational attainment, occupation, household income, infant's gestational age, date of birth, sex) was obtained using a questionnaire. Mother's information during pregnancy (weight and height at booking, history of gestational diabetes mellitus, gravida, weight at each antenatal visit) was obtained from patient card. Pre-pregnancy BMI and gestational weight gain were calculated. Habitual food intakes during pregnancy was assessed using a semi-quantitative food frequency questionnaire and dietary patterns were constructed using principal component factor analysis. Maternal intelligence was assessed using Raven's Standard Progressive Matrices. Post-natal depression was assessed using Edinburgh Postnatal Depression Scale (EPDS) at 6 months, infant temperament using Revised Infant Behaviour Questionnaire (IBQ-R) and home environment quality was assessed using Infant Toddler HOME Inventory (IT-HOME) at 12 months. Mothers were interviewed on infant feeding practices, including milk and complementary feeding. Infant's dietary intakes at 6-24 months were obtained through 24-hour dietary recall interview with mothers, and dietary diversity at 12-24 months based on indicators for assessing Infant and Young Child Feeding (IYCF) practices, were determined. Anthropometric measurements (weight and length) were conducted at 6-24 months, and weight-for-age (WAZ), length-for-age (LAZ), and weight-for-length (WLZ) status were determined. Cognitive development was assessed using Bayley-III at 6-24 months.

P-trend for growth from birth to 24 months and cognitive development from 6 to 24 months were analysed using repeated measures ANOVA for continuous variables and chi-square test for linear-by-linear association for categorical variables. Individual Growth Curve (IGC) modelling was conducted using Linear Mixed Methods to determine the longitudinal growth trajectory from birth to 24 months and cognitive development trajectory from 6 to 24 months. Univariate logistic regression analysis was conducted to determine factors associated with growth status (underweight, stunting, overweight/obesity) at 24 months and was used as selection criteria (p<.25) for inclusion of variables in the multivariate logistic regression analysis. Different variables were adjusted for different factors (e.g., for pre-natal factors and underweight, data were adjusted for monthly household income, infant's sex and gestational age, for nutrient intakes and underweight, data were adjusted for monthly household income, infant's sex and total energy intake). Univariate linear regression was conducted to determine factors associated with cognitive development at 24 months and was used as selection criteria (p<.25) for inclusion of variables in the multivariate linear regression analysis. Different variables were adjusted for different factors (e.g., for socio-demographic factors, data were adjusted for infant's birth weight, for pre-natal factors, data were adjusted for mother's educational level, infant's sex and birth weight). Significance level was determined at p<.05.

There were 53.0% boys and 47.0% girls. The mean gestational age was 38.68 weeks (*SD*=1.14) and the prevalence of low birth weight (LBW) was 7.7%. A linear decreasing trend was observed in the WAZ (p-trend<.01) and LAZ (p-trend<.01). For WLZ, an increasing trend was observed (p-trend<.01), from birth to 24 months. The prevalence of underweight, stunting, wasting, and overweight/obesity at 24 months was 15.4%, 17.1%, 5.1% and 9.4%, respectively. There was also a linear increase in cognitive development from 6 to 24 months, although at 12 months the increment was small and the mean cognitive composite score was lower than at any other ages. The prevalence of cognitive delay at 24 months was 6.8%.

Being underweight at 6, 12, and 18 months were associated with higher risk of underweight at 24 months. Higher birth weight, Adj OR=0.13, 95%CI [0.02, 0.92], and higher intake of iron at 18 months, Adj OR=0.80, 95%CI [0.64, 0.99], were associated with lower risk for underweight at 24 months. Conversely, being LBW increases the risk of underweight at 24 months, as using categorical data did not change the findings. There was no significant association between socio-demographic factors, other pre-natal factors (e.g., maternal height, birth length) and post-natal factors (e.g., maternal postnatal depression, maternal intelligence, infant temperament, home environment quality and other nutrients) with underweight at 24 months. Higher maternal height, Adj OR=0.01, 95%CI [0.01, 0.16], and longer birth length, Adj OR=0.72, 95%CI [0.53, 0.98], were associated with lower risk for stunting at 24 months. Being stunted at 6, 12, and 18 months, were associated with higher risk for stunting at 24 months. There was no significant association between socio-demographic factors, other pre-natal factors (e.g., GWG), and post-natal factors (e.g., maternal postnatal depression, maternal intelligence, infant temperament, exclusive breastfeeding duration, dietary diversity and nutrient intakes) with stunting at 24 months. Higher dietary

diversity score at 24 months, Adj OR=1.78, 95%CI [1.03, 3.07], and being overweight/obese at 6, 12, and 18 months, were associated with higher risk for being overweight/obese at 24 months. There was no significant association between socio-demographic factors, pre-natal factors (e.g., maternal pre-pregnancy BMI, dietary pattern during pregnancy) and other post-natal factors (e.g., maternal intelligence, home environment quality and nutrient intakes) with overweight/obesity at 24 months.

Sex, father's years of education, maternal intelligence, home environment quality, WAZ status at 12 and 18 months, LAZ status at 24 months, and cognitive composite score at 6-18 months, were found to be significant predictors of cognitive development at 24 months ($p<.05$). There was no significant association between monthly household income, pre-pregnancy BMI, dietary pattern during pregnancy, dietary diversity, and nutrient intakes, with cognitive development at 24 months. Therefore, ensuring proper growth and provision of cognitively stimulating home environment are important in the first 2 years of life.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

FAKTOR-FAKTOR AWAL KEHIDUPAN YANG BERKAITAN DENGAN TUMBESARAN DAN PERKEMBANGAN KOGNITIF BAYI DI USIA 24 BULAN DI SEREMBAN, MALAYSIA

Oleh

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Dua tahun pertama kehidupan adalah waktu yang terpenting untuk tumbesaran dan perkembangan. Pendedahan kepada persekitaran yang buruk boleh menjejaskan kesihatan dan prestasi kognitif untuk jangka masa panjang. Kajian kohort ini dijalankan bagi mengenalpasti faktor-faktor awal kehidupan yang berkaitan dengan tumbesaran dan perkembangan kognitif bayi di usia 24 bulan. Seramai 117 pasangan ibu-anak telah diikuti dari usia 6 hingga 24 bulan. Latar belakang sosio-demografi (umur ibubapa, etnik, tahap pendidikan, pekerjaan, pendapatan isi rumah, umur gestasi bayi, tarikh lahir dan jantina bayi) telah diambil melalui borang soal selidik. Maklumat ibu semasa kehamilan (berat dan tinggi pra-kehamilan, sejarah diabetes semasa kehamilan, bilangan kehamilan, berat pada setiap lawatan antenatal) telah diambil dari kad pesakit. IJT pra-kehamilan and kenaikan berat badan sewaktu kehamilan telah dikira. Pengambilan makanan lazim semasa kehamilan telah didapati melalui soal selidik kekerapan pengambilan makanan berbentuk semi-kuantitatif, dan corak pengambilan diet dikenalpasti melalui analisis faktor komponen utama. Tahap kecerdasan ibu telah diuji dengan menggunakan *Raven's Standard Progressive Matrices*. Kemurungan selepas bersalin melalui soal selidik EPDS, kelakuan bayi melalui soal selidik IBQ-R dan kualiti persekitaran rumah didapati melalui soal selidik IT-HOME. Ibu ditemu ramah mengenai amalan pemberian makanan kepada bayi, merangkumi penyusuan dan makanan pelengkap. Pengambilan makanan bayi didapati melalui temu ramah ingatan diet 24-jam bersama ibu, dan kepelbagaian diet bayi di usia 12-24 bulan ditentukan berdasarkan panduan IYCF. Pengukuran antropometri dijalankan di usia 6-24 bulan dan status berat-untuk-umur (WAZ), panjang-untuk-umur (LAZ) dan berat-untuk-panjang (WLZ) ditentukan. Perkembagan koginitif di usia 6-24 bulan diuji menggunakan Bayley-III.

Analisis *p-trend* bagi pertumbuhan dari kelahiran sehingga 24 bulan, dan bagi perkembangan kognitif dari 6 hingga 24 bulan, dilakukan menggunakan *repeated measures ANOVA* bagi pemboleh ubah berterusan dan *chi-square test for linear-by-linear association* bagi pemboleh ubah kategorikal. Model IGC juga dibina menggunakan *Linear Mixed Methods* bagi mengkaji lintasan longitudinal bagi pertumbuhan dari kelahiran sehingga 24 bulan dan bagi perkembagan kognitif dari 6-24 bulan. Analisis *Univariate Logistic Regression* dilakukan bagi mengenalpasti faktor-faktor berkaitan dengan status tumbesaran (kekurangan berat badan, kebantutan, dan berlebihan berat badan/obesiti) pada 24 bulan, dan digunakan sebagai asas pemilihan pemboleh ubah (*p*<.25) untuk dimasukkan ke dalam analisis *Multivariate Logistic Regression*. Pemboleh ubah yang berbeza dikawal dalam analisis perkaitan antara faktor yang berlainan dengan status tumbesaran (contohnya, untuk faktor pre-natal, pendapatan isi rumah, jantina bayi dan umur gestasi dikawal, manakala untuk factor nutrien, pendapatan isi rumah, jantina bayi dan jumlah pengambilan tenaga seharian dikawal). Analisis *Univariate Linear Regression* dilakukan bagi mengenalpasti faktor-faktor berkaitan dengan perkembangan kognitif pada 24 bulan, dan digunakan sebagai asas pemilihan pemboleh ubah (*p*<.25) untuk dimasukkan ke dalam analisis *Multivariate Linear Regression*. Pemboleh ubah yang berbeza dikawal dalam analisis perkaitan antara faktor yang berlainan dengan perkembangan kognitif (contohnya, untuk faktor sosiodemografi, berat kelahiran bayi dikawal, manakal untuk faktor pre-natal, tahap pendidikan ibu, jantina bayi dan berat kelahiran bayi dikawal). Tahap signifikan ditetapkan pada *p*<.05.

Seramai 53.0% lelaki dan 47.0% perempuan telah terlibat di dalam kajian ini. Min usia hasil kandungan adalah 38.68 minggu (*SD*=1.14) dan peratusan berat badan lahir rendah (BBLR) adalah 7.7%. Terdapat tren penurunan secara linear pada WAZ (*p*-trend<.01) dan LAZ (*p*-trend<.01), manakala tren kenaikan secara linear didapati pada WLZ (*p*-trend<.01), dari lahir hingga 24 bulan. Peratusan kekurangan berat badan, kebantutan, kesusutan dan berlebihan berat badan/obesiti pada 24 bulan, masing-masing adalah sebanyak 15.4%, 17.1%, 5.1% dan 9.4%. Perkembangan kognitif bayi dari 6 hingga 24 bulan juga meningkat secara linear, walaubagaimanapun pada usia 12 bulan, kenaikkan skor kognitif adalah kecil dan min komposit skor didapati rendah berbanding di lain-lain usia. Peratusan kelewatan perkembangan kognitif pada usia 24 bulan adalah sebanyak 6.8%.

Kekurangan berat badan pada 6-18 bulan didapati meningkatkan risiko kekurangan berat badan pada 24 bulan. Semakin tinggi berat badan semasa lahir, Adj OR=0.13, 95%CI [0.02, 0.92], dan semakin tinggi pengambilan zat besi pada 18 bulan, Adj OR=0.80, 95%CI [0.64, 0.99], semakin rendah risiko kekurangan berat badan pada 24 bulan. Sebaliknya, BBLR meningkatkan risiko kekurangan berat badan pada 24 bulan. Tiada perubahan dalam dapatan kajian apabila pemboleh ubah kategorikal digunakan. Tiada perkaitan antara faktor sosiodemografi, lain-lain faktor pre-natal (contohnya, ketinggian ibu dan panjang lahir) dan fakor post-natal (contohnya, kemurungan selepas bersalin, tahap kecerdasan ibu, kelakuan bayi, kualiti persekitaran rumah dan lain-lain nutrien) dengan kekurangan berat badan pada 24 bulan. Semakin tinggi ketinggian ibu, Adj OR=0.01, 95%CI [0.01, 0.16], dan semakin tinggi panjang semasa lahir, Adj OR=0.72, 95%CI [0.53, 0.98], didapati menurunkan risiko kebantutan pada 24 bulan. Kebantutan pada 6-18 bulan didapati meningkatkan risiko kebantutan pada 24 bulan. Tiada perkaitan antara factor sosiodemografi, lain-lain faktor pre-natal (contohnya, kenaikkan berat badan semasa mengandung), dan faktor post-natal (contohnya, kemurungan selepas bersalin, tahap kecerdasan ibu, kelakuan bayi, tempoh penyusuan susu ibu secara ekslusif, kepelbagaian diet dan pengambilan nutrien) dengan kebantutan pada 24 bulan. Semakin tinggi skor kepelbagaian diet pada 24 bulan, Adj OR=1.78, 95%CI [1.03, 3.07], dan berlebihan berat badan/obes pada 6-18 bulan, meningkatkan risiko berlebihan berat badan/obesiti pada 24 bulan. Tiada perkaitan antara faktor sosiodemografi, factor pre-natal (contohnya, IJT pra-kehamilan, corak pengambilan diet semasa kehamilan) dan lain-lain faktor post-natal (contohnya, tahap kecerdasan ibu, kualiti persekitaran rumah dan pengambilan nutrien) dengan risiko berlebihan berat badan/obesity pada 24 bulan.

Jantina, jumlah tahun pendidikan bapa, tahap kecerdasan ibu, kualiti persekitaran rumah, status WAZ pada 12 dan 18 bulan, status LAZ pada 24 bulan, dan komposit skor kognitif pada 6-18 bulan, merupakan faktor-faktor yang dapat meramalkan perkembangan kognitif pada usia 24 bulan ($p<.05$). Tiada perkaitan antara pendapatan isi rumah, IJT pra-kehamilan, corak pengambilan diet semasa kehamilan, dan pengambilan nutrien, dengan perkembangan kognitif pada usia 24 bulan. Oleh itu, adalah penting bagi memastikan pertumbuhan yang sihat dan penyediaan persekitaran rumah yang dapat merangsang fikiran dalam 2 tahun pertama kehidupan.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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≈	Approximately equal to
=	Equal to
et al.,	And others
Adj OR	Adjusted Odds Ratio
ANOVA	Analysis of Variance
B	Beta
CI	Confidence Interval
F	F-test
M	Mean
n	Sample size
OR	Odds Ratio
p	p-value
p-trend	p for linear trend
r	Pearson Product-Moment Correlation
SD	Standard Deviation
SE	Standard Error
t	Independent sample t-test
$Z_{1-\alpha/2}$	Standard errors associated with confidence interval
$Z_{1-\beta}$	Standard errors associated with power
α	Alpha error
χ^2	Chi-square test
AGA	Appropriate-for-Gestational Age
ALA	Alpha Linoleic Acid
ALSPAC	Avon Longitudinal Study of Parents and Children

BMI	Body Mass Index
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
DDS	Dietary Diversity Score
DP	Dietary Pattern
EPDS	Edinburgh Postnatal Depression Scale
GA	Gestational Age
GDM	Gestational Diabetes Mellitus
GH	Growth Hormone
GWG	Gestational Weight Gain
HAD	Height-for-Age Difference
HAZ	Height-for-Age
HMOs	Human Milk Oligosaccharides
HOME	Home Observation for Measurement of the Environment
IBQ-R	Revised Infant Behaviour Questionnaire
IGF-1	Insulin-like Growth Factor 1
IOM	American Institute of Medicine
IPH	Institute for Public Health Malaysia
IQ	Intellectual Quotient
IT-HOME	Infant Toddler HOME Inventory
IYCF	Infant and Young Child Feeding
KK	Klinik Kesihatan
LA	Linoleic Acid
LAZ	Length-for-Age
LBW	Low Birth Weight
LC-PUFA	Long-chain Polyunsaturated Fatty Acids

LGA	Large-for-Gestational Age
LMICs	Low- and Middle-Income Countries
MAL-ED	Malnutrition and Enteric Infections: Consequences for Child Health and Development
MDD	Minimum Dietary Diversity
MDI	Mental Development Index
MOH	Ministry of Health Malaysia
NBW	Normal Birth Weight
NCDs	Non-Communicable Diseases
PUFA	Polyunsaturated Fatty Acids
RNI	Recommended Nutrient Intakes
SEANUTS	South East Asian Nutrition Survey
SEP	Socio-economic Position
SES	Socio-economic Status
S-FFQ	Semi-quantitative Food Frequency Questionnaire
SGA	Small-for-Gestational Age
SPM	Standard Progressive Matrices
UNICEF	United Nations International Children's Emergency Fund
UPM	Universiti Putra Malaysia
USDA	United States Department of Agriculture
USM	Universiti Sains Malaysia
WAZ	Weight-for-Age
WHO	World Health Organization
WHZ	Weight-for-Height
WLZ	Weight-for-Length

CHAPTER 1

INTRODUCTION

1.1 Introduction

Nutrition during pregnancy to the first 2 years of life has been demonstrated to have long-term effects on adult health and risk of non-communicable diseases (Koletzko et al., 2012). There are critical periods when the system and organs of the human body are plastic and sensitive to the environment, and most of them occur in utero. Brain, liver and immune systems, however, remain plastic after birth. Plasticity enables the body to adapt in response to the environmental conditions that occur during development (Barker, 2004). An insult or exposure to adverse environment that occurs during a critical or sensitive period of development may have long-term effects on tissue structure or function, which is known as early life ‘programming’ (Lucas, 2005). During the critical period of development, when the environment is compromised, the limited resources will be allocated according to the hierarchy of properties, whereby the development of low-priority organs such as the kidneys and lungs are traded off to protect vital organs such as the brain, which is on top of the hierarchy (Barker, 2012).

Cognitive development refers to the changes in the mental process of acquiring, storing, manipulating, retrieving and utilizing information over the course of development (Galotti, 2011). In the first 2 years of life, cognitive development revolves around the development of sensory-motor abilities. This is because the earliest regions of the brain to mature are those associated with visual control, balance and motor abilities (Hughes & Bryan, 2003). Rapid development of the brain occurs in the first 2 years of life. During this period the brain has a high degree of neuronal plasticity, making it more receptive to the presence or absence of environmental stimuli (Georgieff et al., 2015). Nurturing care is defined as a stable environment that is sensitive to children’s health and nutritional needs, with opportunities for early learning, responsive caregiving and protection from adversities (Britto et al., 2017). It plays an important role in the development of the brain and adaptations during the period of high degree of neuronal plasticity (Britto et al., 2017).

Child development occurs in stages and is a maturational and interactive process that results in increasing perceptual, motor, cognitive, language, socio-emotional and self-regulation skills (Black et al., 2017). These skills provide the foundation for competencies in academics, behavioural, socio-emotional and economic accomplishments, and developmental potential refers to the acquisition of these skills in the early years (Black et al., 2017). The period between birth and 5 years of age is an important period where children develop their cognitive skills to maintain attention, understand and follow direction, communicate with others and solve progressively more complex problems (McCoy et al., 2016). Development of social and emotional competencies, such as the ability to get along with others and independently manage negative emotions is also crucial in achieving the developmental milestones. It is estimated that 43% of children under 5 years of age in the low- and middle-income countries (LMICs) are at risk of not reaching their developmental potential (Black et al., 2017).

Children with poor cognitive and social competencies at kindergarten or preschool entry (between the age of 3-5 years) may struggle with academic difficulties and are more likely to have social and behavioural problems in later school years (Jeon et al., 2011). This may result in lower educational attainment and earning in adulthood, consequently leading to poverty, which is both a cause and an outcome of poor development (Black et al., 2017). In Malaysia, the prevalence of pre-schoolers with cognitive performance below average was 8.7%, while 2.4% had borderline scores and 0.8% had extremely low cognitive performance (Mohd Nasir et al., 2012). Cognitive development before the age of 8 years was found to be associated with higher number of schooling years among children in Northern Finland, British and Philippines birth cohorts (Peet et al., 2015). An increase in 1 standard deviation of cognitive development score was associated with an increase of 0.22 years of schooling among Finnish children, 0.58 years among British children and 1.08 years among children in the Philippines, after adjusting for socio-economic status and biological confounders (Peet et al., 2015).

Growth in the first 2 years of life is a strong predictor of both adult health and human capital (Victora et al., 2008). Delayed physical growth could limit a child's ability to explore the external environment, thus delaying cognitive development (Rosales et al., 2009). Suboptimal growth, as indicated by stunting, wasting and underweight, has been found to be associated with increased risk of death from infectious diseases in childhood (Black et al., 2013). Based on the Global Nutrition Report 2020, the global prevalence of stunting and wasting among children below 5 years old in 2018 was 21.9% and 7.3%, respectively, while 5.9% of children below 5 were overweight (Development Initiatives, 2020). In Malaysia, the National Health and Morbidity Survey (NHMS) 2016 reported the prevalence of stunting, underweight and wasting among children below 5 years of age was 20.7%, 13.7% and 11.5%, respectively, while 6.0% of the children were overweight (IPH, 2016). Underweight and stunting were more prevalent among younger than older children, with the highest prevalence was among 6 to -11 months old children (17.3%) for underweight and 24 to -35 months old children (23.5%) for stunting (IPH, 2016). Meanwhile, the prevalence of wasting (13.6%) and overweight (7.7%) was highest among older children, aged 48 to -59 months (IPH, 2016).

The early years are an important period for children to achieve their developmental potential. Undernutrition during this period may lead to permanent cognitive deficits as it delays motor development, hence limiting children's exploration of the environment (Martorell & Nguyen, 2010; Prado & Dewey, 2014). As undernutrition is usually coupled with micronutrient deficiencies and increased risk of illness, undernourished children tend to be more lethargic and withdrawn (Martorell & Nguyen, 2010). They may receive less stimulation from caregivers. This is because children's characteristics also determine the level of stimulation that they would receive. For example, caregivers are more likely to respond to initiation of interactions by the child rather than initiate the interactions themselves (Engle & Fernández, 2010). Undernourished children may appear younger than their age and are less likely to be challenged to explore and expand their capabilities by caregivers (Martorell & Nguyen, 2010).

Stunting is a marker of chronic undernutrition as it takes a longer time to develop and recover, while wasting is an index of severity but it can change rapidly (Grantham-McGregor & Ani, 2001). Weight-for-age reflects body weight in relation to chronological age and short-term change in weight-for-age resulted in change in weight-for-height, however, in the absence of wasting, underweight also reflects long-term nutritional experience like stunting (WHO, 1997). Chronic undernutrition is more likely to be associated with cognitive development rather than short-term severity (Grantham-McGregor & Ani, 2001). Stunting before the age of 2 years is a recognized risk factor for poor motor and cognitive development (Black et al., 2013). Although deficit in length-for-age may improve after the age of 2 years, improvement in cognitive functioning remains uncertain (Black et al., 2017). Both low height-for-age and weight-for-age have been found to be associated with 2 times higher risk of poor cognitive performance among school-aged children in Southeast Asia (Sandjaja et al., 2013). Length/height-for-age and weight-for-age at 2 years were also found to be the strongest predictors of schooling among children in the LMICs (Victora et al., 2008).

Childhood obesity has become a global health problem and there is growing evidence that overweight may be associated with poor cognitive performance among children (Guxens et al., 2009). Overweight infants and toddlers are more likely to have motor developmental delay (Cataldo et al., 2016; Neelon et al., 2012; Slining et al., 2010). While, greater central adiposity was associated with later rolling over and sitting up in infants, later age at walking was associated with greater overall adiposity at 3 years of age (Neelon et al., 2012). Infants and toddlers with delayed motor development also tend to have delayed mental development (Cataldo et al., 2016). Increased body weight was reported to be associated with decreased visuospatial organization and general cognitive ability among 8 to 16 years old children in the United States (Li et al., 2008). Severe obesity was associated with higher risk of poor cognitive performance among 6 to 12 years old children in Southeast Asia (Sandjaja et al., 2013). In Malaysia, severely obese children had 2 times higher risk of poor cognitive performance than their normal weight peers (Poh et al., 2019).

1.2 Problem statement

Child development is a complex process that is affected by many factors, including genetics, health and nutrition, child's temperament, proximal environment (e.g., quality of relationship in the family and amount of stimulation in the home) and distal environment (e.g., socio-economic status & culture) (Grantham-McGregor & Ani, 2001). Undernourished children are often exposed to poverty as well as its associated factors such as poor housing and lack of cognitive stimulation in the home (Grantham-McGregor & Ani, 2001). Similarly, overweight/obese children are also exposed to multiple adverse environment, including low family income, low parent education, poor family functioning, poor feeding practices, poor eating behaviour, poor sleep and sedentary lifestyle (Chi et al., 2017). Exposure to multiple adverse conditions may result in poorer cognitive outcomes than any single exposure (Guinosso et al., 2016; Prado & Dewey, 2014).

Socio-economic status (SES) as indicated by parents' education level and household income, is consistently associated with both cognitive (Hamid Jan et al., 2010, 2011; Mohd Nasir et al., 2012; Poh et al., 2019) and academic performance (Anuar Zaini et al., 2005; Mohd Shariff et al., 2000; Ong et al., 2010) of children in Malaysia. However, low SES is both a determinant and a consequence of poor cognitive development (Victora et al., 2008). Low SES is associated with poor foetal growth and stunting in the first 2 years of life. Stunting is associated with poor cognitive development and low educational attainment, which in turn reduced adult income (low SES), thus creating a perpetual cycle (Victora et al., 2008). It is therefore important to include SES when determining factors associated with growth and cognitive development in children.

Breastfeeding has been shown to have a dose-response relationship with intellectual quotient (IQ) in children and adolescents. It is an important factor that can bridge the socio-economic gap in the LMICs, as poor women tend to breastfed longer than rich women (Victora et al., 2016). In 2002, the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) developed a global strategy for infant and young child feeding (IYCF) to improve nutritional status, growth and development, health and survival of infants and young children (WHO, 2009). The duration of exclusive breastfeeding until 6 months of age and continued breastfeeding are included in the IYCF indicators. However, published studies on the associations between exclusive breastfeeding duration with growth and cognitive development of infants in Malaysia are scarce, except for a cross-sectional study that reported infants who were not exclusively breastfed for at least 6 months had higher risk of delay in motor development at 6-12 months of age, but not cognitive development (Sabri et al., 2020). A longitudinal study in Singapore, where the population consists of similar ethnic groups (Malay, Chinese and Indian) as in Malaysia, found that longer breastfeeding duration was associated with better memory and language development in the first 2 years of life (Cai et al., 2015). More studies on exclusive breastfeeding duration and its association with growth (e.g., stunting and overweight/obesity) and cognitive development in the first 2 years of life are needed in Malaysia.

Maternal short stature and poor nutrition during pregnancy are associated with higher risk of intrauterine growth retardation (IUGR) (Victora et al., 2008). In developing countries, low birth weight (LBW) is often a result of IUGR as most of the LBW infants are born at term (≥ 37 weeks of gestation) (Martorell & Nguyen, 2010). In Jamaica, LBW infants were found to have poorer problem solving ability at 7 months old (Gardner et al., 2003) and lower developmental levels at 15 and 24 months old (Walker et al., 2004) compared to normal birth weight (NBW) infants. Birth weight and length are also associated with subsequent growth in childhood (Victora et al., 2008). LBW was found to be a determinant of stunting among infants before 2 years of age in Indonesia (Aryastami et al., 2017), as well as among 2-6 years old children in Malaysia (Murtaza et al., 2018). However, more studies are needed, especially among infants in the first 2 years of life.

About 1 in 5 children under the age of 5 years in the East Asia and Pacific regions is either stunted, wasted or overweight, and in some cases suffers both forms of malnutrition (e.g., stunting and overweight) (UNICEF, 2019). Overweight/obesity which was once thought to be more prevalent among the affluent society has now increased among the poor (UNICEF, 2019). In Malaysia, the prevalence of underweight, stunting and wasting among children under 5 years in 2019 was 14.1%, 21.8% and 9.4%, respectively (IPH, 2020). It was also found that 5.6% of Malaysian children under 5 years were overweight/obese in 2019 (IPH, 2020). Under-nutrition (underweight, stunting and wasting) was more prevalent among children in the rural areas and of families in the bottom 40% (B40) of the household income group in Malaysia (IPH, 2020). The monthly household income of the B40 group ranged from below MYR 980 (< USD 231) (poor) to MYR 4,360 (USD 1,028) (lower-middle income) (Ministry of Economic Affairs, 2018). Although over-nutrition (overweight/obesity) was higher in the urban than rural areas, it was also more common among the B40 children (poor to lower-middle income group) (IPH, 2020). Both under- and over-nutrition could occur in the first 2 years of life and continue throughout childhood. Over-nutrition in childhood may also be a result of over-compensation of growth among children who were under-nourished in the first 2 years of life. However, there is a lack of studies that examine the pattern and timing of growth faltering in the first 2 years of life of Malaysian infants, as well as the association between growth in infancy and growth in early childhood (Wong et al., 2018).

Both stunting/height-for-age (Hamid Jan et al., 2011; Mohd Nasir et al., 2012; Mohd Shariff et al., 2000) and overweight/obesity (Poh et al., 2019; Sandjaja et al., 2013; Tung et al., 2019) were found to be associated with poor cognitive performance and academic achievement of Malaysian children. However, most of the existing studies on cognitive performance and academic achievement in Malaysia were conducted among school-aged children. Studies on cognitive development of infants were limited (Ong et al., 2001; Sabri et al., 2020). All of the previous local studies were of cross-sectional in nature and therefore lack of evidence for temporal association (Al-Mekhlafi et al., 2011; Hamid Jan et al., 2010, 2011; Mohd Nasir et al., 2012; Mohd Shariff et al., 2000; Murtaza et al., 2019; Poh et al., 2019; Sabri et al., 2020; Sandjaja et al., 2013; Tung et al., 2019). It is unknown if under-nutrition in the early life has a long-term impact on cognitive performance of children in Malaysia (e.g., stunting at 6 months and cognitive performance at 2 years).

Immediate home environment and care provided by parents and caregivers is the single most powerful context of the nurturing care that could bridge the gap in child development (Britto et al., 2017). Many young children in the LMICs do not receive adequate cognitive stimulation and learning opportunities at home (Obradović et al., 2016). Maternal depression is also higher in LMICs (15-20%) than in High Income Countries (HICs) (6-13%), and depressed mothers tend to be less responsive towards their infants than non-depressed mothers (Collins et al., 2017). Maternal intelligence (McCormick et al., 2019; Ronfani et al., 2015) and infant temperament (Engle & Fernández, 2010) may also contribute to the level of stimulation that the child will receive. However, there is no comprehensive study that examines the interactions between home environment, maternal and child factors, growth and cognitive development of infants in Malaysia. The quantity and quality of stimulation, support, and structure available to a child in the home environment plays an important role in cognitive development (Bradley, 2015). The assessment of home environment measures the extent to which the environment in the home contains experiences that would promote child development and well-being (Bradley, 2015). Evidence that shows the persistent effect of early life adversities (e.g., poor home environment at 12 months) towards cognitive development in later childhood (e.g., at 2 years) is also absence in Malaysia. Therefore, comprehensive studies that include both maternal and child factors, as well as home environment in the early years are needed in determining factors associated with cognitive development in children.

1.3 General objectives

To determine the associations between early life factors with growth and cognitive development of infants at 24 months.

1.4 Specific objectives

1. To determine:
   i. Socio-demographic factors (sex, parent's educational attainment, monthly household income)
   ii. Pre-natal factors (mother's pre-pregnancy BMI, maternal height, gestational weight gain, maternal glycaemia status during pregnancy, dietary pattern in the third trimester, maternal intelligence, birth weight and length)

iii. Post-natal factors (infant feeding practices, infant dietary intake, infant temperament, maternal post-natal depression and home environment)

of infants.

2. To identify the trends of growth and cognitive development in the first 2 years of life.
3. To determine factors (socio-demographic, pre-natal and post-natal) associated with growth status (under- and over-nutrition) at 24 months.
4. To determine factors (socio-demographic, pre-natal and post-natal) associated with cognitive development at 24 months.
5. To determine the association between growth (under- and over-nutrition) with cognitive development at 24 months.

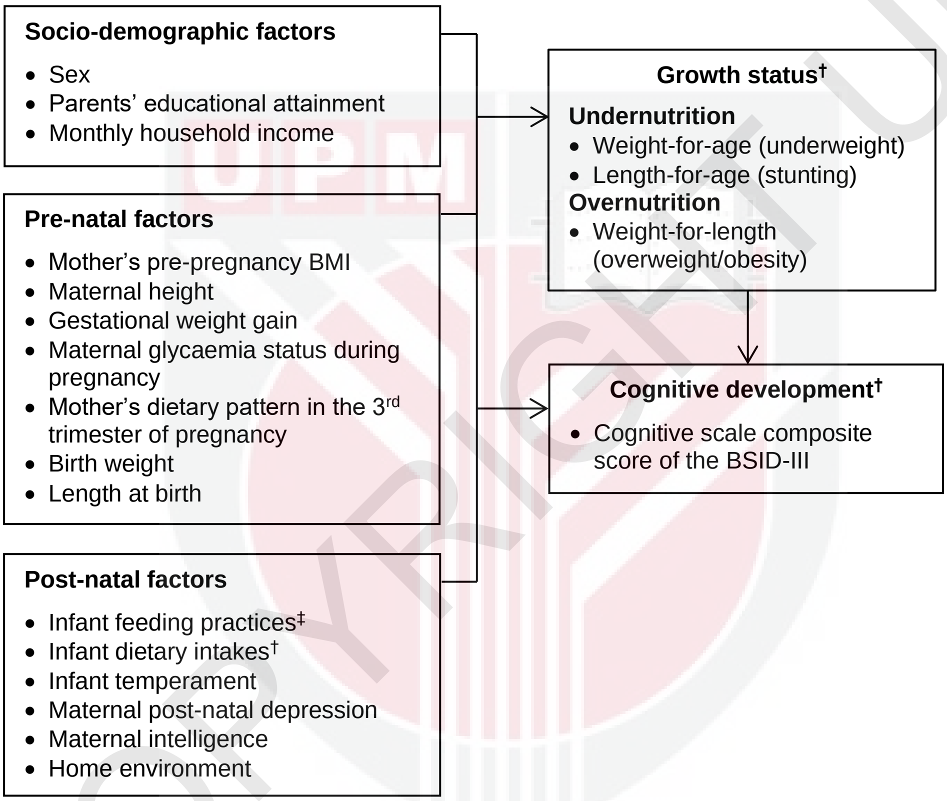
1.5 Hypotheses

1. There are significant negative associations between socio-demographic, pre-natal, post-natal factors, and growth status, specifically under-nutrition, and positive associations with over-nutrition at 24 months.
2. There are significant positive associations between socio-demographic, pre-natal, post-natal factors, and cognitive development at 24 months.
3. There is a significant negative association between growth status (under- and over-nutrition) and cognitive development at 24 months.

1.6 Research conceptual framework

Figure 1.1 shows the conceptual framework of this study. The independent variables are grouped into socio-demographic, pre-natal and post-natal factors. The dependent variables are growth status as indicated by weight-for-age (WAZ), length-for-age (LAZ) and weight-for-length (WLZ), and cognitive development as measured using the cognitive scale of the Bayley Scale of Infant and Toddler Development, 3rd edition (BSID-III), which includes assessment on sensorimotor development, exploration and manipulation, object relatedness, concept formation and memory.

The study examined the trends of growth from birth to 24 months and cognitive development from 6 to 24 months, and determined the associations between socio-demographic, pre-natal and post-natal factors with growth status and cognitive development at 24 months. In this study, for under-nutrition, only associations between independent variables with underweight (WAZ < -2 *SD*) and stunting (LAZ < -2 *SD*) were assessed. The WLZ indicator was only used to determine the associations between independent variables and overweight/obesity (WLZ > +1 *SD*). Wasting (WLZ < -2 *SD*) was not assessed as chronic undernutrition is more likely to be associated with cognitive development than acute undernutrition (Grantham-McGregor & Ani, 2001). It is hypothesized that socio-demographic, pre-natal and post-natal factors are associated with growth status, specifically underweight and stunting (undernutrition) and overweight/obesity (over-nutrition) at 24 months. Socio-demographic, pre-natal and post-natal factors were also hypothesized to be associated with cognitive development of the infants at 24 months. The association between growth status (under- and over-nutrition) and cognitive development was also examined, and it is hypothesized that growth status (under- and over-nutrition) is associated with cognitive development at 24 months.



[†]Repeatedly measured at 6, 12, 18 and 24 months
[‡]At 6 months, milk feeding, introduction of complementary foods (age, first food); Dietary diversity was repeatedly measured at 12, 18 and 24 months

Figure 1.1: Conceptual framework of the study

1.7 Significance of the study

The first 2 years of life is recognized as the most important period for growth and development. Under- and over-nutrition during this period may have substantial effects on health and cognitive functioning in later childhood and adulthood. Children who experienced undernutrition in early life may have higher risk for non-communicable diseases (NCDs). For example, LBW infants (undernutrition in the pre-natal life) may have higher risk for undernutrition (stunting, underweight and wasting) in childhood and cardiovascular diseases in adulthood. Undernourished children may also experience catch-up growth that could be associated with overweight and obesity in later life. Malaysia is experiencing nutrition transition, where the prevalence of overweight and obesity is increasing, while undernutrition is persistent. More children are becoming overweight and obese, and NCDs such as hypertension and type II diabetes mellitus are becoming more common among children and adolescents. At the same time, the prevalence of undernutrition such as stunting remains relatively high among the children. Therefore, it is important to determine whether undernutrition before 2 years of age is associated with overweight and obesity in early childhood (at 2 years).

Infancy is an important period, where experience and skills acquired during this time could provide the platform for learning in later childhood. Children who are undernourished tend to be lethargic and are less likely to explore their environment than healthy children. Studies have shown that the timing of undernutrition is important in determining the strength of association between undernutrition and cognitive performance. This cohort study of infants would be able to identify at which time point (between 6-24 months) does stunting predicts cognitive development at 24 months.

Although there is increasing evidence to support the negative association between overweight/obesity and cognitive performance, the evidence is not as strong as for the effect of undernutrition. In some studies, only severe obesity was associated with poor cognitive performance. Among infants, overweight/obesity has been associated with later achievement of motor milestones. Examination of the association between overweight/obesity and cognitive development of infants in this cohort study may add information to the growing knowledge and would be able to demonstrate if there is a temporal association between overweight/obesity and cognitive development.

The quality of early learning opportunities in the home environment is an important factor that contributes to cognitive development. Studies have found that good home environment quality may attenuate the negative impact of undernutrition on cognitive development. It is possible that good home environment quality may also attenuate the negative association between overweight/obesity and cognitive development. Thus, examining this factor would provide useful information for the direction of future intervention to improve cognitive performance of under- and over- nourished children.

Maternal health and behaviours play important roles in growth and development of infants. Maternal obesity, gestational diabetes and high-fat diet have been associated with high birth weight in infants. Studies have reported that infants of obese mothers tend to have higher adiposity and BMI than those of normal weight mothers. Stunting often begins in utero and mothers with short stature tend to give birth to stunted infants. This cohort study would be able to demonstrate the association between maternal weight status, height and dietary patterns during pregnancy with growth of infants in the first 2 years of life, therefore, providing an evidence-based recommendation for pregnant mothers to ensure healthy growth of their infants.

Maternal mental health is important in cognitive development of infants. Mothers who are depressed tend to be less responsive to their infants and depression may also lead to early cessation of breastfeeding. Longer duration of breastfeeding is associated with better cognitive development. Infants with more intelligent mothers may have better cognitive development than their counterparts. Mothers with higher intelligence may have higher educational attainment, have more knowledge on infant feeding and involve in more cognitively stimulating activities (e.g., reading books). Maternal intelligence may also represent genetic inheritance, in which infants with more intelligent mothers may have more advance cognitive development as they might inherit the intelligence level from their mothers, making the learning process easier for them. Apart from that, children's temperament may also evoke different responses from caregivers, hence different level of stimulation. Therefore, by including these factors, this study would be able to provide a comprehensive examination of factors associated with cognitive development of infants in Malaysia. The prospective design of this study would also enable the determination of cause-and-effect factors of growth and cognitive development in the first 2 years of life. The patterns of growth and cognitive development measured at each time point (6, 12, 18 and 24 months) in this study would also be able to determine the sensitive period for growth and cognitive development, where intervention could be effective.

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LIST OF PUBLICATIONS

Nurliyana AR, Mohd Shariff Z, Mohd Nasir MT, Gan WY, Tan KA. (2020). Early growth and home environment are associated with cognitive development in the first year of life of Malaysian infants. *Early Human Development*, 140, 104890. doi: 10.1016/j.earlhumdev.2019.104890.

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