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Associations of Maternal Vitamin D Status and Feeding Practices with the Development of Allergic Diseases and Malnutrition among Infants in Selangor and Kuala Lumpur, Malaysia

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Associations of Maternal Vitamin D Status and Feeding Practices with the Development of Allergic Diseases and Malnutrition among Infants in Selangor and Kuala Lumpur, Malaysia

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Abstract

Allergic diseases and malnutrition are two of the most common and earliest developing health issues in early childhood. The high prevalence is concerning because of the implications of allergic diseases and malnutrition on long-term health and well-being of the infants. This study aims to determine the associations of maternal vitamin D status during late pregnancy and feeding practices with the development of allergic diseases and malnutrition in infants during the first year of life.

This prospective cohort study was conducted at six selected government health clinics at the state of Selangor and Federal Territory of Kuala Lumpur, Malaysia. A total of 535 pregnant women were recruited during their third trimester and their child was followed up prospectively until 12 months of age. A blood sample was collected from the pregnant women to determine their serum 25(OH)D concentrations. After delivery, 380 mother-infant pairs completed the follow-up at 3, 6, and 12 months. During the postnatal follow-up, information on feeding practices and allergy development in infants were obtained from the mother through face-to-face interviews. Infant's anthropometric data were extracted from medical records. Malnutrition in terms of stunting, wasting, underweight, and overweight was determined by z-scores for length-for-age, weight-for-length, weight-for-age, and BMI-for-age, respectively, based on WHO Child Growth Standards 2016. At 12 months of age, serum samples were collected from the infants to determine their sensitisation against food allergens.

Vitamin D insufficiency and deficiency were observed in 48.8% and 42.8% of the pregnant women, respectively. Almost half of the mothers complied with the WHO infant feeding recommendations to exclusively breastfeed their child for at least 6 months (46.6%) and 97.1% introduced complementary foods at 6 months. Only 10.5% of infants met minimum dietary diversity (MDD) at 6 months and the proportion increased to 54.5% at 12 months. A total of 27.6% of the infants had eczema, 20.8% had parent-reported food allergy, 3.8% had IgE-mediated food allergy, and 27.4% had food sensitisation during the first year of life. The prevalence of stunting, wasting, underweight, and overweight at 12 months was 16.3%, 7.6%, 11.6%, and 1.8%, respectively. After adjusting for potential confounders, study sites, and mother-infant pairs clustering effect, results from a multivariable generalised linear mixed model showed that deficient maternal vitamin D level during late pregnancy was associated with higher risk of parent-reported food allergy in infants (aOR = 1.76, 95% CI = 1.01-3.05). Higher risk of food sensitisation was found in infants who met MDD at 6 months (aOR = 2.31, 95% CI = 1.02-5.20). No associations were found for maternal vitamin D status and other feeding practices with eczema, IgE-mediated food allergy, and malnutrition. Parent-reported food allergy was associated with higher odds of wasting in infants (aOR = 2.54, 95% CI = 1.15-5.60), while no associations were found for other allergic outcomes with malnutrition. Results of the multivariable linear mixed models showed that exclusive breastfeeding until 6 months were associated with lower WAZ (B = -0.09, 95% CI = -0.49, -0.26), LAZ (B = -0.23, 95% CI = -0.44, -0.03), WLZ (B = -0.34, 95% CI = -0.57, -0.12) and BAZ (B = -0.32, 95% CI = -0.52, -0.13) in infants at 12 months of age. After adjusting for potential confounders, the structural equation model

showed that the relationships between maternal vitamin D status during late pregnancy (-0.29, 95% CrI = -0.55, -0.05) and wasting in infants (0.27, 95% CrI = 0.07, 0.51) was fully mediated by parent-reported food allergy.

In conclusion, the present study suggests that maternal vitamin D deficiency during late pregnancy is a risk factor for the development of food allergy in infants during the first year of life. Food allergy is a mediator in the relationships between maternal vitamin D status and wasting. Further studies are needed to verify the results of the present study.

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Thank you.

Certification

I, Woon Fui Chee, declare that this thesis submitted in fulfilment of the requirements for the conferral of the degree Doctor of Philosophy, from the University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. This document is submitted as part of a joint PhD program between the University of Wollongong and the University Putra Malaysia.

Woon Fui Chee
13 April 2020

Statement of Verification

This statement verifies that this thesis entitled "Associations of Maternal Vitamin D Status and Feeding Practices with the Development of Allergic Diseases and Malnutrition among Infants in Selangor and Kuala Lumpur, Malaysia" is part of the Mother and Infant Cohort Study (MICOS). The candidate, Woon Fui Chee, under the guidance of her supervisors, took primary responsibility for the design and conduct of the study, data entry and analysis, drafting and finalising all manuscripts submitted to the relevant journals for publication.

Woon Fui Chee (PhD Candidate)
13 April 2020

Professor Marijka Batterham (Primary Supervisor)
13 April 2020

List of Abbreviations

AAP	American Academy of Pediatrics
AGA	Appropriate for Gestational Age
ASCIA	Australasian Society of Clinical Immunology and Allergy
aOR	Adjusted Odds Ratio
BAZ	BMI-for-age z-score
BIC	Bayesian Information Criterion
BMI	Body Mass Index
BSA	Body Surface Area
CD	Cluster of Differentiation
CF	Complementary Feeding
CI	Confidence Interval
CLA	Chemiluminescent Assay
CrI	Credibility Interval
DD	Doctor Diagnosed
DHS	Demographic Health Surveys
DOHaD	Developmental Origins of Health and Disease
EAACI	European Academy of Allergy and Clinical Immunology
EBF	Exclusive Breastfeeding
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology, and Nutrition
FcεRs	High-affinity IgE Receptors
GLMM	Generalised Linear Mixed Model
GUSTO	Growing Up in Singapore Towards Healthy Outcomes
GWG	Gestational Weight Gain
HMO	Human Milk Oligosaccharides
HUKM	Hospital National University of Malaysia
IFN	Interferons
IgE	Immunoglobulin E
IL	Interleukins
IOM	Institute of Medicine
IPH	Institute of Public Health
IQR	Interquartile Range
ISAAC	International Study of Asthma and Allergies in Childhood
IYCF	Infant and Young Child Feeding
JKEUPM	Ethics Committee for Research Involving Human Subjects, Universiti Putra Malaysia
LAZ	Length-for-age z-score
LU	Luminescence Units
MCH	Maternal and Child Health

MCMC	Markov Chain Monte Carlo
MDD	Minimum Dietary Diversity
MHC	Major Histocompatibility Complex
MICOS	Mother and Infant Cohort Study
MOH	Ministry of Health Malaysia
MREC	Medical Research and Ethics Committee
MSAI	Malaysian Society of Allergy and Immunology
NCCFN	National Coordinating Committee on Food and Nutrition of Malaysia
NHMS	National Health and Morbidity Survey
NPANM	National Plan of Action for Nutrition of Malaysia
OFC	Oral Food Challenge
OR	Odds Ratio
PPV	Positive Predictive Values
PR	Parental Reports
RCT	Randomised Controlled Trial
RM	Ringgit Malaysia
RNI	Recommended Nutrient Intakes
SDG	Sustainable Development Goals
SDS	Standard Deviation Scores
SEI	Sun Exposure Index
SES	Socioeconomic Status
SEM	Structural Equation Modelling
sIgE	Serum Allergen-specific Immunoglobulin E
SPT	Skin Prick Test
SR	Self-report
TGF	Transforming Growth Factor
Th	T-helper
TNF	Tumour necrosis factor
Tregs	Regulatory T Cells
UKMMC	Universiti Kebangsaan Malaysia Medical Center
UN	United Nations
UNICEF	United Nations Children's Fund
UVB	Ultraviolet B
WAZ	Weight-for-age z-score
WLZ	Weight-for-length z-score
WHO	World Health Organization
WPDC	Working Party Diagnostic Criteria
1,25(OH)2D	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D

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Glossary of Terms

Allergic March	The natural history of allergic manifestation, which progresses from one allergy to another allergy over time (Weinberg, 2005).
Allergy	An abnormal over-reaction of the body initiated by specific immunologic mechanisms through exposure to substances that are usually not harmful to the human body (Johansson et al., 2004).
Atopy	An individual shows an excessive IgE response towards a specific allergen, which has been documented by IgE antibodies in serum or by a positive skin prick test (Johansson et al., 2014).
Barker's Hypothesis	Environmental influences during the foetal and early infant life can permanently programme the growth and metabolism of the body, thereby influences the development of chronic diseases in later life (Barker, 2001).
Critical period	A time during development when growth is intense and any deficiencies during this period could lead to long-term and irreversible consequences (Buklijas, 2014).
Developmental Origins of Health and Disease	Exposure to pre- and postnatal environmental influences can contribute to child's development and disease susceptibility in the long term (Gluckman & Hanson, 2006).
Eczema	A chronic and recurrent inflammatory skin disease which is characterised by abnormally dry skin and intense itching (Pawankar et al., 2013).
Food allergy	An adverse immune reaction to food proteins which is associated with a variety of symptoms involving the skin, respiratory tracts, and gastrointestinal tracts (Waserman & Watson, 2011)
Hypersensitivity	Objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons (Johansson et al., 2004, p.833).
IgE-mediated Allergy	An allergic reaction that is mediated by the production of IgE antibodies (Johansson et al., 2004).
Malnutrition	Failure of the body to obtain the appropriate amount of energy and nutrients to maintain health and function of the tissues and organ. Malnutrition in the form of wasting, stunting, and underweight can result from an inadequate intake of energy and nutrients while overweight and obesity is a result of excessive intake of energy and nutrients (WHO, 1997).
Minimum Dietary Diversity	Infants should consume at least four food groups in a day when complementary foods were introduced at 6 months of age (WHO, 2008).
Programming	A stimulus or insult that occurred during the critical or sensitive periods in early life can pose a long-term or lifetime effects on a range of physiological functions and structures of an individual (Lucas, 1991).
Sensitisation	The production of IgE antibodies towards an allergen, which has been demonstrated by a positive IgE serum test or skin prick test, without the presence of clinical symptoms (O'Hehir et al., 2016).
Vitamin D Deficiency	Serum 25(OH)D concentrations of below 30 nmol/L (IOM, 2011).
WHO Infant Feeding Recommendations	Infants are recommended to be exclusively breastfed for the first 6 months of life and complementary foods should be introduced at 6 months along with continued breastfeeding until 2 years of age or beyond (WHO, 2001).

Chapter 1

Introduction

1.1 Background of Study

Early life is the most important period in human life cycle that can permanently shape an individual body's structure, function, and metabolism in ways that determines the susceptibility to disease later in adulthood (Barker, 2001; Gluckman & Hanson, 2006). The early life period from conception to birth involves rapid growth and development of the fetus and is particularly sensitive to alterations of the intrauterine environment (Barker, 2001; Lucas, 1991). Previous studies demonstrates that an altered intrauterine environment is associated with an increased risk of non-communicable diseases such as obesity and heart disease later in life (Barker, Osmond, Golding, Kuh, & Wadsworth, 1989; Hoffman, Reynolds, & Hardy, 2017; Wang, Wang, Kong, Zhang, & Zeng, 2010). Infancy, especially during the first year of life, is another early life period that involves rapid growth in stature and brain development, as well as immune system development that strongly influences long-term health (Gillman, 2010; Gleeson & Cripps, 2004). Observational studies and randomised controlled trials suggest that rapid weight gain during the first year of life is associated with obesity, high blood pressure, and diabetes in later life (Bansal et al., 2008; Dunger, Salgin, & Ong, 2007; Gillman, 2010). Recognising the importance of the early life period in lifelong health and well-being, primary prevention strategies and interventions targeting the modifiable risk factors during this critical period are essential to prevent the early manifestation of the health problems or their progression into adulthood.

Allergic diseases and malnutrition are two of the most common and earliest developing health issues during the first 2 years of life (Ijarotimi, 2013; Zheng, Yu, Oh, & Zhu, 2011). Allergy is an abnormal over-reaction of the body initiated by specific immunologic mechanisms through exposure to substances that are usually not harmful to the human body (Johansson et al., 2004). Eczema and food allergy are the first manifestations of allergic diseases, which usually appear during the first 2 years of life and are interrelated (Hill & Spergel, 2018; Martin et al., 2015; Tham & Leung, 2019). Eczema, also known as atopic dermatitis, is a chronic and recurrent inflammatory skin disease which is characterised by abnormally dry skin and intense itching (Pawankar, Canonica, Holgate, Lockey, & Blaiss, 2013). Food allergy refers to an adverse immune reaction to food proteins which is associated with a variety of symptoms involving the skin, respiratory tracts, and gastrointestinal tracts (Waserman & Watson, 2011). Eczema and food allergy are important risk factors for the development of other allergic diseases such as asthma and allergic rhinitis in later childhood (Alduraywish et al., 2016; Gustafsson, Sjöberg, & Foucard, 2000; Hill, Grundmeier, Ram, & Spergel, 2016). The progression of eczema and food allergy to asthma and allergic rhinitis is known as atopic march (Hill & Spergel, 2018). The global prevalence of allergic diseases has increased dramatically in the last few decades and have affected about 20.0% of the world's population (Pawankar, Canonica, Holgate, Lockey, & Blaiss, 2013). Globally, about 5.0-34.0% of the infants

are affected by eczema during the first 2 years of life (Hennessy et al., 2018; Jones, Palmer, Zhang, & Prescott, 2012) and the prevalence of food allergy in infants during the first year of life ranged from 1.9% to 11.0% (Kristinsdóttir et al., 2011; Peters et al., 2017). Allergic diseases not only can affect patient's quality of life, but also pose significant economic and social burden towards patients and their families (Ang, Cecilia, Monika, & Wee, 2014; Pawankar, 2014).

Malnutrition, another common childhood health issues, refers to a condition that occurs due to lack of proper nutrition, which contributes to the inadequate or excessive intake of energy and nutrients. Inadequate intake of energy and nutrients leads to malnutrition in the form of wasting (low weight-for-height), stunting (low height-for-age), and underweight (low weight-for-age), while excessive intake leads to overweight and obesity (high body mass index [BMI]-for-age) (de Onis & Blossner, 1997). Malnutrition starts to develop as early as during the in-utero period. It is estimated that 20.5 million (14.6%) newborns in the world were suffered from low birth weight in the year 2015 and 91.0% were from the low- and middle-income countries (Blencowe et al., 2019). Globally, 21.9%, 13.4%, 7.3%, and 5.9% of the children under 5 years of age are stunted, underweight wasted, and overweight, respectively (UNICEF, WHO, & The World Bank, 2019). A key target under Sustainable Development Goal (SDG) adopted by the United Nations (UN) is to end all forms of malnutrition by 2030 (target 2.2) (UN, 2015). However, the global prevalence of malnutrition in children under 5 years remains high and the progress of reduction in malnutrition has been slow (UNICEF et al., 2019). Malnutrition is one of the leading causes of death among children under-five and may lead to long-term consequences such as delayed cognitive development, impaired growth, and increased vulnerability to chronic diseases in later life (Ijarotimi, 2013).

1.2 Problem Statement

The prevalence of allergic diseases which were previously on the rise in the developed countries seems to have reached a plateau or even started to decrease (Deckers et al., 2012; Malik, Tagiyeva, Aucott, McNeill, & Turner, 2011; Wennergren, 2011). Conversely, emerging evidence shows that allergic disease prevalence, which was previously low, in the developing countries continues to rise (Leung, Wong, & Tang, 2018). The prevalence of eczema in children aged 6-7 years in Malaysia has increased over the past few years from 9.5% in 1995 to 12.6% in 2001 (Williams et al., 2008). A small-scale cross-sectional study in Kuala Lumpur, Malaysia found a prevalence of 16.7% for eczema in 48 infants aged 1-2 years (Goh, Keshavarzi, & Chew, 2018). It is estimated that the prevalence of allergic diseases will continue to increase for the next two decades due to rapid economic growth and urbanisation in the Asian countries, such as Malaysia (Wong, Leung, & Ko, 2013). However, in Malaysia, allergic diseases including eczema and food allergy are not accorded the attention and priority that it needs. Local study assessing the prevalence of eczema in infants is scarce, with only one study conducted in infants under 2 years of age on eczema (Goh et al., 2018) and there is no available data on food allergy prevalence in infants. More studies are therefore

needed to understand the extent of eczema and food allergy problems in Malaysia, so that preventive strategies can be taken to halt the atopic march.

In addition to allergic diseases, undernutrition and overnutrition coexist among children in Malaysia (IHSR, 2020). In Malaysia, the under-five prevalence of stunting, underweight, wasting, and overweight was 21.8%, 14.1%, 9.7%, and 5.6%, respectively, according to the latest National Health and Morbidity Survey (NHMS) (IHSR, 2020). In particular, 22.1% of the infants under 2 years of age were stunted, 14.7% were underweight, 11.2% were wasted, and 4.1% were overweight, respectively (IPH, 2016a). Compared to NHMS 2015 (wasting 8.0%, stunting 17.7%, and underweight 12.4%), there has been a significant increase in the under-five prevalence of undernutrition, while the prevalence of overweight has reduced by 1.1% (IPH, 2015). The issues of child malnutrition have been addressed in the National Plan of Action for Nutrition of Malaysia (NPANM) and nutrition promotion programs and interventions have been implemented to cope with the issues (MOH, 2016a). Although preventive measures have been implemented, the burden of under-five child malnutrition in Malaysia has not improved and has been reported as having no progressed or even worsened according to the latest Global Nutrition Report 2018 (Development Initiatives, 2018). Thus, further study is needed to determine the risk factors for childhood malnutrition in Malaysia so that preventative measures targeting the specific risk factors can be taken to tackle the malnutrition problem effectively.

Findings from previous studies have suggested a relationship between allergic diseases and malnutrition (Berents et al., 2017; El-Heis et al., 2018). Restricted foetal growth leads to a higher risk of allergic diseases during infancy, and in turn, infants with allergic diseases demonstrate growth faltering in early childhood which causes a vicious cycle (Beck et al., 2016; Berents et al., 2017; Chong, Wright, Goh, Meyer, & Rao, 2018; El-Heis et al., 2018; Flammarion et al., 2011). Considering the vulnerability to allergic diseases and malnutrition during early life and their long-term health consequences, it is important to seize the window of opportunity for primary prevention and break the vicious cycle of allergic diseases and malnutrition.

The development of allergic diseases and malnutrition can be explained through the complex interplay between genetic inheritance and environmental exposures (Albuquerque, Nóbrega, Manco, & Padez, 2017; Campbell, Boyle, Thornton, & Prescott, 2015; Workalemahu et al., 2018). Although part of the increasing prevalence of allergic diseases and malnutrition in childhood can be explained by genetic predisposition, increased attention has been focused on the role of nutrition in the pre- and postnatal environment during the first 1000 days of life (Baïz et al., 2019; Dewey, 2016; Garcia-Larsen et al., 2018). As nutrition is a modifiable risk factor, targeting the role of early life nutrition in the development of allergic diseases and malnutrition in children is essential for identifying potential primary prevention strategies.

Vitamin D deficiency is one of the common micronutrient deficiencies during pregnancy (Fiscaletti,

Stewart, & Munns, 2017). Vitamin D deficiency is prevalent worldwide, with the prevalence ranging from 21.0% to 84.0% in the Asia-Pacific region (Wilson et al. 2018; Kanatani et al., 2019), 10.0% to 43.7% in the Americas region (Chrisostomo et al., 2018; Flood-Nichols, Tinnemore, Huang, Napolitano, & Ippolito, 2015), 27.4% to 94.2% in the European region (Baki Yildirim & Koşar Can, 2019; Rodríguez-Dehli et al., 2015) and 55.8% to 81.0% in the Middle Eastern region (Al-Musharaf et al., 2018; Badfar, Shohani, Mansouri, Soleymani, & Azami, 2017). In Malaysia, different prevalence of maternal vitamin D deficiency has been reported across states, ranged from 37.0% in the state of Kelantan (Jan Mohamed, Rowan, Fong, & Loy, 2014) to 82.2% in the state of Selangor (Lee et al., 2020). Vitamin D has long been recognised for its importance in musculoskeletal health (Wintermeyer et al., 2016). In recent years, vitamin D has gained increased attention for its role in non-skeletal outcomes such as allergic diseases and malnutrition (Mirzakhani, Al-Garawi, Weiss, & Litonjua, 2015; Moon, Davies, Cooper, & Harvey, 2020; Pereira-Santos, Costa, Assis, Santos, & Santos, 2015). Several birth cohorts have provided some evidence on the associations of maternal serum 25-hydroxyvitamin D [25(OH)D] levels with allergic diseases (Blomberg et al., 2017; Chiu et al..,2015; Gale et al., 2008; Weisse et al., 2013) and malnutrition (Morales et al., 2015; Toko et al., 2016) in children, respectively. In the US, children of mothers with low prenatal serum 25(OH)D levels had a higher risk of eczema between 0-3 years of age (Blomberg et al., 2017). The Taiwan birth cohorts found that higher maternal serum 25(OH)D levels were associated with a lower risk of food sensitisation in children at 2 years of age and eczema at 4 years of age (Chiu et al., 2015). Conversely, results from the UK and Germany birth cohorts suggested that high maternal serum 25(OH)D levels increased the risks of eczema, food allergy, and food sensitisation in children during the first 2 years of life (Gale et al., 2008; Weisse et al., 2013). In terms of malnutrition, previous studies found that infants of mothers with low serum 25(OH)D levels during pregnancy were more likely to become stunted at birth (Toko et al., 2016) and overweight at 1 year of age (Morales et al., 2015). Some randomised controlled trials have assessed the effects of maternal vitamin D supplementation during pregnancy on infant's allergy risk (Chawes et al., 2014; 2016; Goldring et al., 2013; Litonjua et al., 2016; 2020) and growth (Roth et al., 2018; Sahoo, Katam, Das, Agarwal, & Bhatia, 2017), respectively, but no significant effects were reported. Considering the high prevalence of vitamin D deficiency in pregnant women worldwide and inconsistent findings in previous studies, more studies are needed to confirm the causal role of maternal vitamin D levels in the development of allergic diseases and malnutrition in infants.

Apart from adequate nutrition during the prenatal period, optimal infant feeding during the first 2 years of life is important to promote healthy growth and resistance to infection and disease in children (WHO, 2009). Global recommendations for optimal infant feeding include infants should be exclusively breastfed for 6 months with the introduction of complementary foods after 6 months and continued breastfeeding until 2 years old or beyond (WHO/UNICEF, 2003). In addition to complementary feeding, it is recommended that infants should consume at least four food groups in a day to achieve the minimum dietary diversity (WHO, 2008). Despite the benefits of optimal infant

feeding, improper feeding practices are widespread around the world. While more than half of infants aged 0-5 months worldwide were not been on exclusively breastfed, 31.0% infants aged 6-8 months were not given complementary foods on time, and more than two-third of the infants aged 6-24 months (71.0%) did not meet the minimum dietary diversity (UNICEF, 2019). Previous studies have provided some findings on the associations between infant feeding practices and the development of allergic diseases (Gao et al., 2019; Goldsmith et al., 2016; Roduit et al., 2012; Roduit et al., 2014; Taylor-Robinson, Williams, Pearce, Law, & Hope, 2016); however, findings remain inconclusive. While a cohort study conducted in the UK showed that breastfeeding for ≥ 6 months and early introduction of complementary foods at ≤ 4 months was associated with an increased risk of childhood eczema (Taylor-Robinson et al., 2016), but no significant association was reported in the Melbourne HealthNuts study (Goldsmith et al., 2016). In contrast, a cohort study conducted in China showed that introduction of complementary foods < 6 months was associated with a higher risk of food allergy in infants (Gao et al., 2019). Another cohort study conducted in five European countries reported that introduction of a less diverse food group between 3-12 months of age was associated with an increased risk of eczema in infants (Roduit et al., 2012).

Meanwhile, findings from previous studies also suggested that infant feeding practices may influence the risk of malnutrition in children. Evidence from two systematic reviews suggest that breastfeeding is protective against childhood obesity (Horta & Victoria, 2013; Yan, Liu, Zhu, Huang, & Wang, 2014). Findings from the cross-sectional studies showed that introduction of complementary foods at ≥ 6 months and at least 4 food groups were associated with decreased risk of malnutrition in children (Udoh & Amodu, 2016; Huynh, Huynh, Nguyen, Do, & Khanh Tran, 2019). A prospective cohort study in Australia showed that children who were introduced with complementary foods at ≤ 4 months were more likely to become overweight and obese (Mannan, 2018). Knowing the important role of infant feeding practices on allergic diseases and malnutrition, further studies are needed to determine whether the optimal infant feeding practices can reduce the risk of allergic diseases and malnutrition in children.

Overall, research suggests that allergic diseases and malnutrition are correlated and can occur simultaneously during the first two years of life (Beck et al., 2016; Berents et al., 2017; Chong et al., 2018). Considering the long-term consequences of allergic diseases and malnutrition in early life (Ang et al., 2014; Hill & Spergel, 2018; Ijarotimi, 2013), there is a need for developing interventions to simultaneously prevent both allergic diseases and malnutrition targeting their shared risk and protective factors. As discussed earlier, maternal vitamin D status in the prenatal period and infant feeding in the postnatal period can influence the risk of allergic diseases and malnutrition in children, respectively (Blomberg et al., 2017; Mannan, 2018; Morales et al., 2015; Taylor-Robinson et al., 2016). However, comparison across studies can be difficult due to methodology differences in terms of the study population, length of follow-up, and assessment of variables. In addition, most researches have focused on direct relationships between single exposure (maternal vitamin D status or infant feeding practices) and outcome (allergic diseases or malnutrition). Studies

assessing multiple and interrelated relationships of maternal vitamin D levels and infant feeding practices with allergic diseases and malnutrition simultaneously are lacking.

Thus, the present study aims to answer the following research questions:

1. What is the prevalence of maternal vitamin D insufficiency and deficiency during late pregnancy, compliance with the WHO infant feeding recommendations, allergic diseases, and malnutrition in infants during the first year of life?
2. Is maternal vitamin D status during late pregnancy and infant feeding practices associated with the development of allergic diseases and malnutrition in infants during the first year of life?
3. Are there any interrelationships between maternal vitamin D status during late pregnancy, infant feeding practices, development of allergic diseases, and malnutrition in infants during the first year of life?

1.3 Significance of the Study

The present study provides an update on the vitamin D status of third trimester pregnant women in Malaysia. Despite the adverse pregnancy outcomes of vitamin D deficiency, data on vitamin D status among Malaysian pregnant women is limited and the issue of vitamin D deficiency in pregnancy is not targeted in the latest National Plan of Action for Nutrition of Malaysia III (NPANM III) (MOH, 2016). Thus, vitamin D status reported in the present study is important to inform public health policy development to optimise vitamin D level during pregnancy. Furthermore, this study provides an update on the prevalence of compliance with WHO infant feeding recommendations in terms of exclusive breastfeeding, introduction of complementary foods, and minimum dietary diversity in Malaysian urban children at age 1 year. Data reported in this study allows for the comparison of infant feeding practices within countries, identify populations at risk, and assess the impacts of interventions that had previously implemented.

This study updates the prevalence of eczema and food allergy and inform about the common food allergens in Malaysian infants during the first year of life. The prevalence reported in this study can raise public awareness of the allergy issues in Malaysia. Action should be taken to understand the scope of the problems to provide epidemiological clues for prevention. Meanwhile, the prevalence of malnutrition in terms of stunting, underweight, wasting, and overweight reported in this study provides an insight into what extent that the NPAMN III (MOH, 2016) targets have been met and indicates the need for continued efforts to improve the nutritional status in infants.

This study contributes to the expanding body of scientific literature regarding the shared risk and protective factors for allergic diseases and malnutrition in infants during the first year of life. The cohort study design of this research can provide evidence for the causal relationships between maternal vitamin D status during late pregnancy and feeding practices with the development of

allergic diseases and malnutrition in infants. Interventions targeting the modifiable nutrition-related risk factors during the window of opportunity are important for primary prevention of allergic diseases and malnutrition. A better understanding of the interrelationships between maternal vitamin D status during late pregnancy, infant feeding practices, development of allergic diseases, and malnutrition may help to develop cost-effective interventions to simultaneously prevent allergic diseases and malnutrition in infants.

1.4 Objectives

1.4.1 General Objective

To determine the associations of maternal vitamin D status during late pregnancy and infant feeding practices with the development of allergic diseases and malnutrition in infants during the first year of life.

1.4.2 Specific objectives

1. To determine the prevalence of maternal vitamin D insufficiency and deficiency and its associated factors among pregnant women in late pregnancy.
2. To determine the prevalence of compliance with WHO infant feeding recommendations, allergic diseases, and malnutrition in infants during the first year of life.
3. To determine the associations of maternal vitamin D status during late pregnancy and infant feeding practices with the development of allergic diseases and malnutrition in infants during the first year of life.
4. To determine the interrelationships between maternal vitamin D status during late pregnancy, infant feeding practices, development of allergic diseases, and malnutrition in infants during the first year of life.

1.5 Alternative Hypotheses

Ha1: Maternal vitamin D deficiency during late pregnancy and non-compliance with WHO infant feeding recommendations are associated with a higher risk of allergic diseases and malnutrition in infants during the first year of life.

Ha2: There is an interrelationship between maternal vitamin D status during late pregnancy, infant feeding practices, development of allergic diseases, and malnutrition in infants during the first year of life.

1.6 Conceptual Framework

Figure 1.1 presents the conceptual framework of the present study. The conceptual framework is developed according to the theory of "developmental origins of health and disease" (DOHaD) which emphasises the role of pre- and post-natal environment in child's health and risk of diseases (Gluckman & Hanson, 2006). The dependent variables in this study are allergic diseases and malnutrition. Allergic diseases and malnutrition are the most common and earliest developing health issues in early childhood (Ijarotimi, 2013; Zheng et al., 2011). Eczema and food allergy usually co-exist and are the first manifestations of allergy that often begin in the first few years of life (Hill & Spergel, 2018; Tham & Leung, 2019). Malnutrition exists in multiple forms, namely stunting, underweight, wasting, and overweight (de Onis & Blossner, 1997). Recent evidence suggests that allergic diseases and malnutrition are correlated and can occur simultaneously during the first 2 years of life (Beck et al., 2016; Berents et al., 2017; Chong et al., 2018).

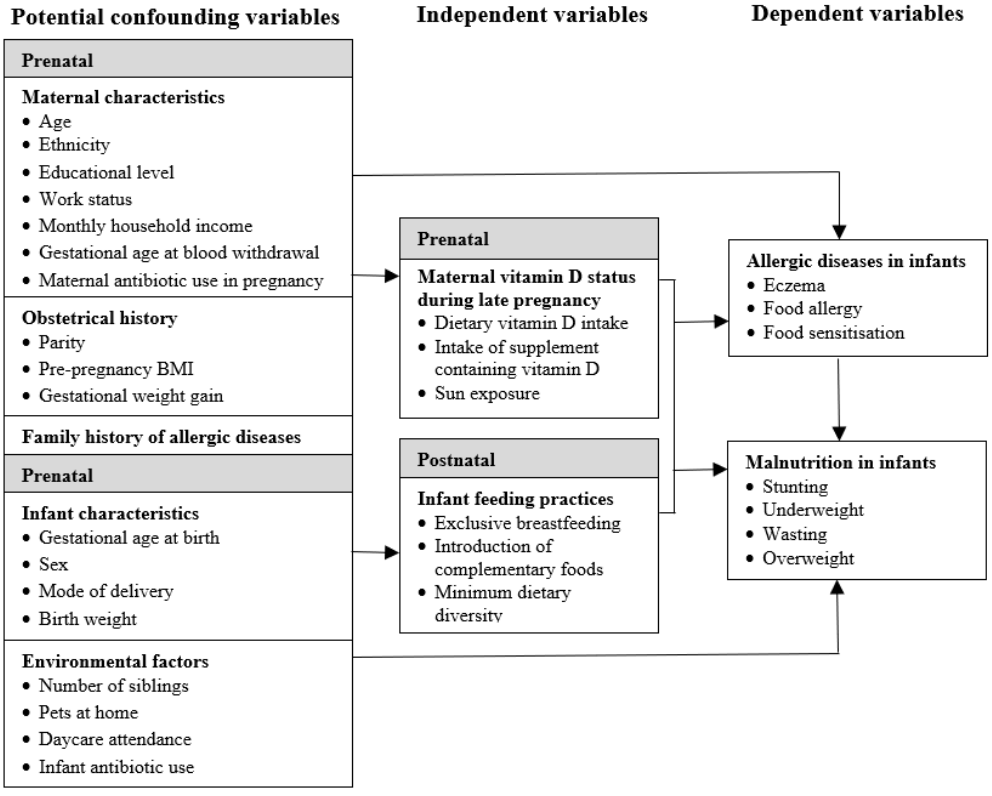


Figure 1.1. Conceptual framework

The independent variables in this study include maternal vitamin D status during late pregnancy and infant feeding practices. Findings from several birth cohorts suggested that both lower and higher levels of maternal prenatal vitamin D levels were associated with eczema and food allergy risk in children (Blomberg et al., 2017; Gale et al., 2008; Weisse et al., 2013). Significant associations between maternal vitamin D levels and childhood malnutrition were also observed in several birth cohorts (Eckhardt, Gernand, Roth, & Bodnar, 2015; Morales et al., 2015; Toko et al., 2016). In terms of infant feeding practices, breastfeeding duration, age at introduction of complementary

feeding, and minimum dietary diversity have been linked to the development of childhood allergic diseases (Gao et al., 2019; Lodge et al. 2015; Roduit et al., 2012) and malnutrition (Udoh & Amodu, 2016; Vail et al., 2015; Woo et al., 2013), respectively.

Observational cohort studies are susceptible to confounding, which can threaten the validity of the study results (Greenlandn & Morgenstern, 2001; Klein-Geltink, Rochon, Dyer, Laxer, & Anderson, 2007). Confounding occurs when the association between exposure and outcome is influenced by other factors, which are not in the causal pathway between exposure and outcome (Klein-Geltink et al., 2007). Thus, it is important to rule out the confounding effect by suitable adjustment for potential confounding factors, which can be identified based on conceptual justification and statistical analysis (Nurmatov, Nwaru, Devereux, & Sheikh, 2012). Nurmatov and colleagues (2012) have proposed a list of potential confounding factors which should be considered in observational studies assessing the association between nutrition and childhood allergies. According to Nurmatov et al. (2012), the confounding factors based on conceptual justification include maternal and child characteristics (maternal age, child's sex, family history of atopy disease, parity, birth weight, gestational age at birth, and mode of delivery), socioeconomic status (education, income, occupation), environmental exposures (use of antibiotics during pregnancy and early life, pets at home, and exposure to day care during infancy), and dietary factors (breastfeeding), while the confounders based on statistical analysis include maternal BMI, ethnicity, and season of ascertainment of dietary factors. By referring to the list of confounders suggested by Nurmatov et al. (2012) and previous studies assessing the association between nutrition and childhood malnutrition (Hanieh et al., 2014, Mannan, 2018; Morales et al., 2015; Moschonis et al., 2017; Toko et al., 2016; Woo et al., 2013), the potential confounding factors included in the present study are: (1) maternal characteristics (age, ethnicity, educational level, work status, monthly household income, gestational age at blood withdrawal), (2) obstetrical history (parity, pre-pregnancy BMI, and gestational weight gain), (3) family history of allergic diseases, (4) infant characteristics (gestational age at birth, sex, mode of delivery, and birth weight), and (5) environmental factors (maternal antibiotic use in pregnancy, number of siblings, pets at home, daycare attendance, and infant antibiotic use).

Chapter 2

Literature Review

2.1 Developmental Origins of Health and Disease

Like other living organisms, human beings are "plastic" during their early life and are able to develop in order to adapt to the environment (Barker, 2001). For instance, the unborn baby in the mother's womb is able to receive signals from their mother that prepares them to adapt to the environment they will have to live in. If the mother is malnourished, the unborn baby will receive signals that he or she is in an adverse environment and will respond to the signals by adapting to the environment through the reduction of their body size or metabolism alteration to match forthcoming challenges (Barker, 2001). These adaptations are known as early life programming. The term "programming" refers to the concept that a stimulus or insult that occurred during the critical or sensitive periods in early life can pose a long-term or lifetime effects on a range of physiological functions and structures of an individual (Lucas, 1991). A critical period is a time during development when growth is intense and any deficiencies during this period could lead to long-term and irreversible consequences (Buklijas, 2014).

The epidemiological evidence of a programming effect on humans, first described by Barker and Osmond in 1986 linked adult disease to in-utero events (Barker & Osmond, 1986). This study demonstrated that adult ischaemic heart disease was associated with infant mortality rate and this association was strongly influenced by geographical locations. Different geographical locations represented different living conditions which affect nutrition in early life. They suggested that nutrition during the prenatal and early infancy life might be the key determinants of ischaemic disease in later life and concluded that disturbance during childhood is linked to the risk of disease in adulthood (Barker & Osmond, 1986). Barker and his colleagues followed this observation with a number of studies conducted in Hertfordshire, England and found that children born with low birth weight and had low body weight at the first year were at a higher risk for developing coronary heart disease, high blood pressure, and type II diabetes (Fall et al., 1995; Hales et al., 1991; Osmond et al., 1993). Based on these observations, Barker then proposed the theory of foetal and infant origins of adult disease, or also known as "Barker's hypothesis" that environmental influences during the foetal and early infant life can permanently programme the growth and metabolism of the body, thereby influences the development of chronic diseases in later life (Barker, 2001). However, Barker's study has received several criticisms that some of the important confounding factors, such as social class before and after birth and the mother's smoking status, were not taken into account. In addition, infant weight was used as a proxy for foetal and infant nutrition instead of the actual measurement of maternal and infant's nutritional intake (Paneth & Susser, 1995).

The findings by Barker and his colleagues have been replicated extensively. The theory was later modified to "developmental origins of health and disease" (DOHaD) to better reflect the role of both

the pre- and postnatal environment on child's development and disease susceptibility in the long term (Gluckman & Hanson, 2006). One of the well-known cohort studies that represents the concept of DOHaD is the Dutch Hunger Winter study, which included adults exposed to the Dutch famine of 1944-1945 (Lumey & van Poppel, 2013). Findings from the Dutch famine cohort showed that adults who were exposed in-utero to famine were reported to have a higher risk of hypertension (Stein et al., 2006), higher cholesterol level (Lumey et al., 2009), and type II diabetes (van Abeelen et al., 2012) during middle age. In addition, adults who were exposed to famine during late gestation had a lower birth weight (Lumey et al., 1993), while those exposed during early gestation were more likely to be obese and at a higher risk of coronary heart diseases in adulthood (Roseboom, de Rooij, & Painter, 2006). Similar findings were also reported by famine cohorts in Asian countries. In China, prenatal exposure to famine was associated with a higher risk of type II diabetes (Meng et al., 2018) and exposure to famine during early infancy increased the risk of hypertension during adulthood (Wang et al., 2016). Meanwhile, adults who were exposed in-utero to famine in Bangladesh were more likely to be underweight and hyperglycemic (Finer et al., 2016). To date, most of the DOHaD studies have been conducted in developed countries and increasingly becoming recognised in developing countries. Overall, the consensus from the DOHaD studies is that most of the non-communicable diseases in adulthood are "programmed" early in life, during the first 1000 days of life, starting from conception to around 24 months of age (Barker, 2007). Nutrition is a key player in programming and thus all nutrients received during the first 1000 days of life play an important role in foetal and infant's growth and development, as well as later susceptibility of non-communicable diseases.

Malnutrition and allergic diseases are two of the modern maladies that commonly occur during the first two years of life and pose long-term health effects if left untreated (Ijarotimi, 2013; Zheng et al., 2011). Previous research from the developed countries have applied the DOHaD theory on these maladies and demonstrated that they have their roots during the in-utero period and are correlated with each other (Berents et al., 2017; El-Heis et al., 2018). To date, the double burden of malnutrition which was previously prevalent in the developed countries is now increasingly observed in low- and middle-income countries, including Malaysia (Development Initiatives, 2018). Findings from the latest Global Nutrition Report showed that both women of childbearing age and children under five years of age were suffering from all form of malnutrition (Black et al., 2013; Development Initiatives, 2018). Women who are malnourished are entering pregnancy with adverse nutritional conditions. Nutrition during pregnancy can have a lasting impact on foetal growth and development, as well as immune function (Hoffman et al., 2017; Hsu & Tain, 2019). If the foetus is under adverse nutritional conditions in the womb, they experience intrauterine growth restriction and thus are born with low birth weight and at a higher risk of obesity in adulthood (Eriksson et al., 2001; Yang et al., 2008; Zhou et al., 2018). At the same time, nutritional insults during pregnancy may alter gut microbiota of the pregnant women, which lead to microbial imbalance, also known as dysbiosis (Hsu & Tain, 2019). Dysbiosis of maternal gut microbiota leads to alteration of the pool of bacteria being transferred to the foetus/infant through placenta and breastfeeding at postnatal life, thus

affecting offspring immune system, development of allergic diseases and obesity at later life (Chu et al., 2016; Cukrowska, 2018; Mulligan & Friedman, 2017; Turnbaugh et al., 2006; Turnbaugh et al., 2009).

In summary, increasing evidence supports the concept that the first 1000 days of life is a critical period for nutrition programming. Knowing this, it is important to utilise the DOHaD paradigm to identify the strategies for preventing the two most common childhood ailments, allergy and malnutrition. Lacking of local evidence urges more researches to be conducted to determine the role of early nutrition in childhood allergy and malnutrition.

2.2 Allergic Diseases

2.2.1 Definition

Hypersensitivity is defined as "objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons" (Johansson et al., 2004, p.833). In other words, hypersensitivity occurs when a person's body overreacts to harmless substances. Allergy is a hypersensitivity reaction produces by the body's immune system upon exposure to an allergen (Johansson et al., 2004). Allergen is a substance that can induce an immune response in the body and causes an allergic reaction (Johansson et al., 2004).

Allergy can be either cell-mediated or antibody-mediated. Cell-mediated immunity is an immune response mediated by antigen-specific cytotoxic T cells and the release of cytokines, without involving antibodies. In contrast, an antibody-mediated immunity is an immune response mediated by B lymphocytes through the secretion of antibodies (Hyde, 1995). In most of the cases, an allergic reaction is mediated by the production of immunoglobulin (Ig) E antibodies, which also known as IgE-mediated allergy (Johansson et al., 2004). Some individuals are genetically predisposed to respond to certain allergens, usually proteins, by producing IgE antibodies and are known as atopy. The term "atopy" can only be used when an individual shows an excessive IgE response, which has been documented by IgE antibodies in serum or by a positive skin prick test (Johansson et al., 2014). The allergic symptoms developed by an atopic individual should be referred to as atopic, for instance, atopic eczema. The production of IgE antibodies towards an allergen, which has been demonstrated by a positive IgE serum test or skin prick test, without the presence of clinical symptoms should be referred as sensitisation (O'Hehir, Holgate, & Sheikh, 2016). Allergy can only be confirmed through a combination of detailed history and physical examination, the presence of clinical signs and symptoms, and the production of specific IgE antibodies upon allergen exposure (Nagaraju, 2014).

2.2.2 The Allergic March

The natural history of allergic manifestation, which progresses from one allergy to another allergy over time is called allergic march (Weinberg, 2005). As shown in Figure 2.1, eczema and food allergy are the first manifestation of allergic diseases in infants, follows by asthma, and finally allergic rhinitis in children (Bantz, Zhu, & Zheng, 2014). Some of the allergic diseases may become more prominent with time and persist for many years, while others may see improvements or disappear completely with increasing age (Bantz et al., 2014; Weinberg, 2005).

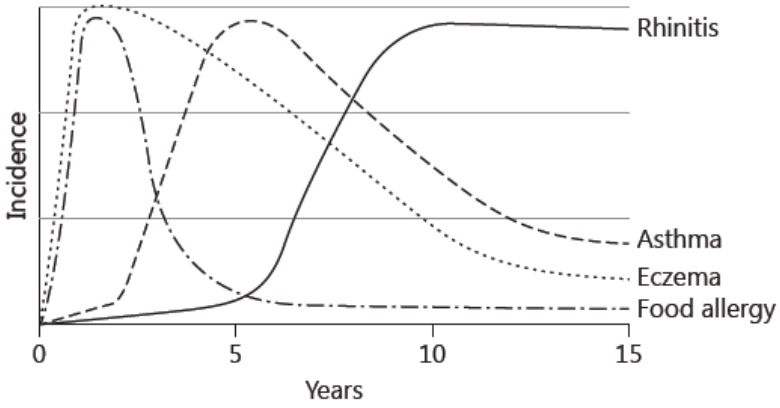


Figure 2.1. Allergic march - progression with age from eczema and food allergy to asthma and rhinitis (Source: Barnetson & Rogers, 2002)

Eczema shows a high incidence in the first few years of life and was proposed as an "entry point" for subsequent allergic diseases such as asthma and allergic rhinitis (Weinberg, 2005). Eczema and food allergy usually co-exist and food allergy has been known as a provoking cause of eczema (Nutten, 2015; Zheng et al., 2011). The concept of the allergic march staring from eczema and food allergy to the development of asthma and allergic rhinitis has been supported by previous cross-sectional and cohort studies. A meta-analysis included 13 cohort studies by Alduraywish et al. (2016) found that food sensitisation in the first 2 years of life was associated with a higher risk of eczema, wheeze/asthma, and allergic rhinitis from 4 to 8 years. A cross-sectional study conducted by Kay et al. (1994) in England reported that 45.0% of the children aged 3 to 11 years developed eczema during the first 6 months of life, 60.0% developed during the first year of life, and up to 85.0% developed before 5 years of age. Similarly, a local study conducted by Yadav and Naidu (2015) among 192 allergic children (≤ 10 years of age) at a private hospital in Malaysia found that eczema was the most common allergic disease among children below 2 years old.

In the United Kingdom, Rhodes and his colleagues (2001) conducted a 22 years prospective cohort study among 100 infants from atopic families at birth. Rhodes and his colleagues found that the prevalence of eczema was highest in children at 1 year of age (20.0%) and then declined to just below 5.0% when the participants reached 22 years old. Over the study period, the prevalence of allergic rhinitis has raised from 3.0% to 15.0%. The prevalence of wheezing increased from 5.0%

during the first year of life to 40.0% at 22 years old. The study found that early sensitisation to hen's egg, cow's milk, or both in the first year of life significantly contributed to the development of adult asthma. Another prospective cohort study conducted in Sweden found that 17.6% of the children had eczema at 1-2 years of age (von Kobyletzki et al., 2012). The study also found that children with eczema were three times more likely to develop asthma and nearly three times more likely to develop rhinitis compared to children without eczema during the 5 years follow-up period. Consistent findings were also reported by Saunes et al. (2012) in a 4-year prospective cohort study at Central Norway that children with eczema at 2 years old were more likely to develop asthma at 6 years compared to children without eczema.

Findings from previous studies suggest that allergic diseases may follow a sequential development and support the idea that there is a link between eczema, food allergy, and later onset of asthma and allergic rhinitis. A study to identify risk factors of eczema and food allergy in early childhood is needed in order to interrupt the allergic march and to prevent the subsequent development of asthma and allergic rhinitis.

2.2.3 Mechanism of Allergic Reaction

Cytokines are the chemical messengers secreted by immune cells in the human immune system to communicate and act on other cells to produce appropriate immune responses. Cytokines consist of a diverse assortment of interleukins (IL), interferons (IFN), and growth factors. Although there are various types of cytokines, it can be generally divided into two groups based on their function: those that are pro-inflammatory and those that are anti-inflammatory. T lymphocytes are the main source of cytokines and are divided into two main subsets based on the presence of cell surface molecules known as CD4 and CD8. T lymphocytes that express CD4 are known as helper T cells, which act as the most prolific cytokine producers. Helper T cells can be further divided into two subsets known as T-helper 1 (Th1) and T-helper 2 (Th2), and the cytokines they produce are known as Th1-type cytokines (IL-12, IFN-γ, TNF-β) and Th2-type cytokines (Il-4, IL-5, IL-6, IL-10, IL-13) (Figure 2.2) (Berger, 2000).

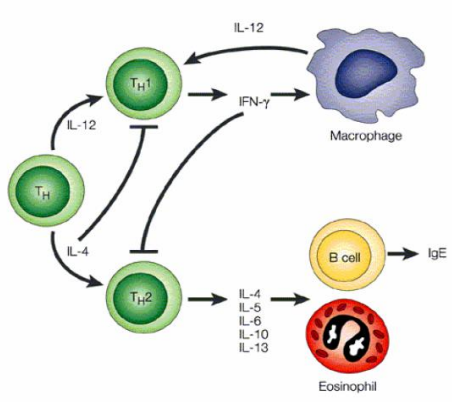


Figure 2.2. T-helper cell differentiation and production of cytokines
(Source: O'Shea, Ma, & Lipsky, 2002).

Th1-type cytokines produce pro-inflammatory responses which are responsible for killing intracellular pathogens and for perpetuating autoimmune responses. Tissue damage may occur if excessive pro-inflammatory responses are produced. Hence, Th-2 type cytokines which produce an anti-inflammatory response are important to counteract the excessive Th1 responses (Berger, 2000). Th-2 type cytokines play an important role in eosinophil activation and IgE production which are necessary for allergic inflammation (Ngoc, Gold, Tzianabos, Weiss, & Celedon, 2005).

An allergic reaction occurs when there is a disturbed balance between Th1 and Th2, which involves three stages; namely, sensitisation, mast cell activation, and late phase reactions (Wood, 2001). When an allergen invades the body, it is immediately processed by the antigen-presenting cells and major histocompatibility complex (MHC) class II molecules in the body. A fragment of the allergen is then presented to the allergen-specific CD4 Th2 cells. Binding of the allergen fragment with the CD4 Th2 cells causes the Th2 cells to proliferate and induces the secretion of IL-4. Secretion of IL-4 promotes the differentiation and proliferation of the allergen-specific B cells and induces cells to produce allergen-specific IgE antibodies. IgE antibodies will then bind to the high-affinity IgE receptors (FcεRs) on mast cells and the mast cells have now become sensitised. The initial exposure to an allergen leads to an increased level of IgE antibodies and usually does not produce any symptoms (Wood, 2001). Once re-exposed to the same allergen, the allergen immediately binds to the allergen-specific IgE antibodies that are bound to the FcεRs on mast cells and cause cross-linking of the IgE antibodies. This will trigger a series of intracellular signalling events that lead to activation of the mast cells, degranulation, and the release of preformed mediators such as histamine, prostaglandins, and cytokines from the mast cell granules. These mediators will cause an inflammatory reaction and generate allergy symptoms (Wood, 2001). The last stage for allergic reaction is known as the late phase reactions. Activated mast cells secrete inflammatory mediators that attract T-cells to mast cells and induce other immune system cells such as basophils, eosinophils, and monocytes to migrate to the affected site. These cells produce inflammatory substances that lead to further inflammatory on the affected site and sometimes might cause prolonged immune activity and tissue damage (Wood, 2001).

2.2.4 Eczema

Eczema (also known as atopic dermatitis) is a common, chronic, relapsing inflammation of the skin which is often observed among young children (Bieber, Leung, El Gamal, & Ivancevich, 2011). Symptoms of eczema vary with age, ranging from mild form such as pityriasis alba (dry and pale patches) to major form such as erythrodermic rash (peeling red rash). In peoples suffer from eczema, moisture lost easily from the skin, causing the skin to dry out and lowered the threshold for itching (Bieber et al., 2011).

Infants usually have facial and patchy or widely distributed eczema. Cheeks of the infants are the first place to be affected by eczema. Lesions generally first appear on the cheeks and are

characterised by dry and red skin with papulovesicular lesions. Scratching of the skin leads to inflammatory and crusty erosions. In toddlers and children from 18 to 24 months onwards, the common sites affected by eczema include flexural areas (antecubital fossa, neck, wrists, and ankles), the nape of the neck, dorsum of the feet, and the hands. Rashes usually begin with tiny raised bumps that become hard and lichenified with inflammatory infiltration when they are scratched. Frequent scratching of the affected skin can lead to the destruction of melanocytes, resulting in areas of pale patches when the inflammation subsides. Eczema may improve during school years and may disappear completely, leaving a sensitive and dry skin. In some cases, eczema may relapse during puberty or adulthood. The symptoms of eczema in adolescents and adults are similar to the childhood phase, characterised by localised inflammation with lichenification of the flexural areas. The commonly affected sites include the neck, upper chest, large joint flexures, and backs of the hands. Facial skin is usually affected on the forehead, eyelids, and perioral region (Bieber et al., 2011).

Data on global prevalence of eczema was assessed in the International Study of Asthma and Allergies in Childhood (ISAAC) with a standardised and validated methodology (Mallol et al., 2013). This data allows direct comparison of eczema prevalence between children from different regions around the world. The ISAAC Phase Three was conducted in 98 countries in the world involving 388811 children aged 6 to 7 years old to determine their prevalence of eczema by using a parent-reported questionnaire (Mallol et al., 2013). Results from the ISSAC showed that the global prevalence of eczema among children was 7.9% (Table 2.1). The prevalence of eczema across regions has shown to vary from 3.0% to 15.5% with the highest in Oceania and lowest in Indian Sub-Continent (Mallol et al., 2013).

The prevalence of eczema in infants ≤ 2 years of age was reported in individual studies conducted across the globe (Table 2.2). In the Asia-Pacific region, the prevalence of eczema ranged from 5.6% (Chuang et al., 2011) to 34.1% (Jones et al., 2012), while the prevalence of eczema in the Europe region ranged from 5.0% (Hennessy et al., 2018) to 20.9% (Alm et al., 2009). The inconsistencies in sample size, age groups, and definition of eczema making comparisons of eczema prevalence across studies difficult.

In Malaysia, the prevalence of eczema among children aged 6 to 7 years old has increased from 9.5% to 12.6% over a 6-year period based on the findings from the ISAAC Phase One and Phase Three studies (Asher et al., 2006). The prevalence of eczema in Malaysian children is on the rise, however data on eczema prevalence in infants is limited. Only one cross-sectional study reported 16.7% prevalence of eczema among 48 infants (1-2 years of age) attending childcare centres in Kuala Lumpur, Malaysia (Goh et al., 2018). The atopic march indicates that eczema peaked during the first few years of life (Weinberg, 2005). Given the increasing prevalence of eczema among children in Malaysia and lacking data of eczema prevalence in infants, more studies assessing eczema prevalence are needed to understand the extent of the eczema problem in Malaysia.

Table 2.1. Global prevalence of eczema in children aged 6-7 years old (Mallol et al., 2013)

Region	Population (n)	Prevalence of eczema (%)
Africa	5865	9.3
Asia-Pacific	59979	9.6
Eastern Mediterranean	40573	4.8
Indian Sub-Continent	50092	3.0
Latin America	93774	9.8
North America	4012	10.1
Northern and Eastern Europe	42548	6.1
Oceania	13888	15.5
Western Europe	77722	8.1
Global total	**388811**	**7.9**

2.2.5 Food Allergy

It is important to distinguish between food allergy and food intolerance when evaluating food allergy. Food allergy is defined as an immune-mediated adverse reaction to food, typically proteins, while food intolerance is defined as a non-immune-mediated adverse reaction to food (Bruijnzeel-Koomen et al, 1995). Food allergy can be further classified into IgE-mediated and non-IgE-mediated. The IgE-mediated food allergy is the most common type of food allergy and is frequently reported in previous studies (Bruijnzeel-Koomen et al, 1995). The most common allergenic foods include cow's milk, soybeans, eggs, peanuts, wheat, fish, shellfish, and tree nuts (Calder, Field, & Gill, 2002). The symptoms of food allergic reactions involve cutaneous manifestations including urticaria and angioedema, gastrointestinal manifestation including mouth and lip pruritus, abdominal pain, vomiting and diarrhoeas, respiratory manifestations including rhinorrhea and wheezing, and anaphylaxis, which is the most severe manifestation of food allergy (Fiocchi & Sampson, 2011).

Food allergy has been known as the "second wave" of the allergic epidemic, following the respiratory allergic diseases, asthma and allergic rhinitis (Prescott & Allen, 2011). Over the past few years, the prevalence of food allergy has increased and affecting up to 10% of the infants and pre-school children in developed countries (Peters et al., 2017). To date, there is growing evidence that the food allergy epidemic has reached the developing countries following economic transition (Leung et al., 2018). While the data on global trends of eczema have been well-documented, high-quality data on the global prevalence of food allergy are lacking (Aït-Khaled et al., 2009; Asher et al., 2006; Lai et al., 2009; Odhiambo et al., 2009). Different definitions and methods have been used across studies to define food allergy and accurate prevalence of food allergy based on the gold standard of oral food challenge is limited (Loh & Tang, 2018; Prescott et al., 2013).

Table 2.2. Global prevalence of eczema in infants aged 6-24 months

Country	Age (months)	Sample size (n)	Prevalence (%)	Method	Reference
Asia-Pacific Region					
Australia (Perth)	12	231	34.1	PR	Jones et al., 2012
China (Changsha)	12	903	25.0	PR	Gao et al., 2019
Thailand	12	4021	7.4	SR	Sangsupawanich et al., 2007
Taiwan	6-18	18773	5.6	PR	Chuang et al., 2011
Korea	< 24	2131	5.9	PR	Ha, Lee, & Yon, 2020
Japan	6-18	46616	16.7	PR	Matsumoto et al., 2019
Singapore	< 18	792	23.6	PR	Loo et al., 2015
Europe Region					
Netherlands (Rotterdam)	12	3019	18.2	PR	Gazibara et al., 2016
Austria, Finland, France, Germany, Switzerland	12	912	15.9	PR	Roduit et al., 2012
France (Nancy & Poitiers)	12	239	10.0	PR	Baiz et al., 2014
Iceland (Cork)	≤ 24	1537	5.0	UK WPDC	Hennessy et al., 2018
Sweden (Western)	12	4921	20.9	PR	Alm et al., 2009

Note: PR: parental report of a doctor diagnosis; SR: self-report by parents; UK WPDC: UK Working Party Diagnostic Criteria

In addition, the food allergy prevalence was reported among children from different age groups, which made comparisons across studies from different countries difficult. Table 2.3 summarises the prevalence of food allergy among children in different countries which was determined based on parental report, diagnosed by a doctor, serum allergen-specific IgE, skin prick test, and oral food challenge. In Western countries, the prevalence of food allergy in children based on oral food challenge ranged from 1.9% (Kristinsdóttir et al., 2011) to as high as 10.4% (Osborne et al., 2011). In developed Asian countries such as Taiwan, Korea, Hong Kong, and Singapore, the prevalence of food allergy ranged from 2.9% (Tham et al., 2018) to 5.3% (Kim et al., 2011). The majority of the data were based on parental reports which may overestimate the prevalence of food allergy in these countries. Only two studies were found from the developing countries, whereby the prevalence of challenged-proven food allergy was 3.8% among children under 2 years of age in China (Chen et al., 2011) and 1.1% among children aged 3-7 years in Thailand (Lao-araya & Trakultivakorn, 2012). Cow's milk, eggs, and peanuts are some of the common food allergens in both Western and Asian countries (Table 2.3).

In Malaysia, there is no food allergy prevalence data in children from the general population and the prevalence of food allergy were only reported among atopic children (Gendeh, Muhjahid, Murad, & Rizal, 2004; Zahedi et al., 2011). In a cross-sectional study conducted at the Otorhinolaryngology clinic, Hospital National University of Malaysia (HUKM), 141 children aged 12 years old and below with allergic rhinitis were skin prick tested to evaluate their sensitisation to 16 common Malaysian foods (Gendeh et al., 2004). Results showed that almost half of the children (48.9%) were sensitised to seafood allergens and the most common seafood allergens were crab (24.8%) and prawn (24.1%). A similar study was conducted by Zahedi et al. (2011) among 580 children aged 5-10 years old with allergic rhinitis attended the Otorhinolaryngology clinic, Universiti Kebangsaan Malaysia Medical Center (UKMMC). The study found that 38.6% of the children showed a positive skin prick test to food allergens and seafood was the most common food allergen. Yadav and Naidu (2015) conducted a study among 192 allergic children aged ≤ 2 years old and 2 to 10 years old attended an allergy clinic in Pantai Hospital Kuala Lumpur. This study revealed that egg and cow's milk sensitisation were common among children aged ≤ 2 years old (60.0% and 44.4%, respectively) and 2-10 years old (26.2% and 25.7%, respectively). Hence, there remains a need to gather data on the prevalence of food allergy to provide an update on the current status of food allergy among children in Malaysia.

2.2.6 Allergy Testing and Interpretation

As the prevalence of allergic diseases is on the rise, more primary care providers are providing or recommending allergy testing for individuals with allergic conditions to ensure accurate diagnosis, identify causative allergens, and provide appropriate treatment (Portnoy, 2011). The diagnosis of allergic diseases starts by taking a clinical history and physical examination (Chokshi & Sicherer, 2016; Pawankar et al., 2013). A detailed clinical history can help to link the developed symptoms

Table 2.3. Global prevalence of food allergy among children (0 - 7 years old)

Country	Age (year)	Sample size (n)	Prevalence (%)							Method	Reference
			Overall	Cow's milk	Egg	Shellfish	Peanut	Fish	Wheat		
Asia-Pacific Region											
Australia	1	2848	10.4	-	8.9	-	3.0	-	-	SPT, OFC	Osborne et al., 2011
China	0-1	477	3.8	1.3	2.5	-	-	-	-	SPT, OFC	Chen et al., 2011
Thailand	3-7	452	1.1	-	-	0.9	-	0.2	-	SPT, sIgE, OFC	Lao-araya et al., 2012
Taiwan	<3	813	3.4	1.1	0.4	1.1	1.1	0.5	-	PR, DD	Wu et al., 2012
Korea	1	1177	5.3	1.7	2.8	0.5	0.7	-	0.1	PR, DD	Kim et al., 2011
Hong Kong	2-7	3677	4.6	0.3	0.4	0.9	0.5	0.3	-	PR, DD	Leung et al., 2009
Singapore	1	902	2.9	0.4	1.8	0.2	0.1	-	0.1	PR, SPT	Tham et al., 2018
Americas Region											
United States	0-2	5429	6.3	2.0	1.0	0.5	1.4	0.3	0.3	PR	Gupta et al., 2011
Europe Region											
United Kingdom	1	969	3.6	0.2	1.4	-	0.3	0.2	-	SPT, OFC	Venter et al., 2006
Denmark	0-6	534	3.7	-	-	-	-	-	-	SPT, sIgE, OFC	Eller et al., 2009
Iceland	1	1341	1.9	0.5	1.4	-	0.2	0.2	0.2	SPT, sIgE, OFC	Kristinsdóttir et al., 2011
Sweden	1-4	2572	6.8	-	-	-	-	-	-	PP, DD	Protudjer et al., 2016

Note: PR: parent-reported; DD: Doctor-diagnosed; SPT: skin prick test; sIgE: serum allergen-specific IgE blood test; OFC: oral food challenge.

with allergen exposures (Pawankar et al., 2013; Portnoy, 2011). When taking a clinical history, information that should be obtained from the patient includes frequency, duration, severity, and seasonal pattern of the symptoms, suspected cause, triggering factors, previous medical history, diet, treatment received, impact of illness, and family history (Pawankar et al., 2013; Rusznak & Davies, 1998). Once the association between symptoms and allergen exposure has been identified based on clinical history, further testing can be done to confirm the suspected triggers through in vivo or in vitro tests (Portnoy, 2011).

2.2.6.1 *In Vivo* Tests

In vivo tests, also known as skin tests can be used to identify the causative allergens for the symptoms. Skin tests measure the reaction of mast cell degranulation when an introduced allergen interacts with the specific IgE antibody bound to mast cell in the skin (Birch & Pearson-Shaver, 2020). There are two types of skin tests, namely, percutaneous test and intracutaneous. A percutaneous test involves pricking the skin, usually on the volar aspect of the forearm or the upper back, using a sterile needle or lancet through the dilute solution of the allergen of interest. Meanwhile, a positive (histamine dihydrochloride or phosphate) and negative control (glycerosaline diluent) are placed on the skin as a comparison for the reaction. The skin reaction is observed after 15-20 minutes. Formation of a wheal at the tested site of at least 3 mm larger than the negative control is considered to be positive (Pawankar et al., 2013). The result of the skin prick test must always correlate with the clinical history. A positive result for both the skin prick test and clinical history confirmed that the symptom is caused by the suspected allergen (Rusznak & Davies, 1998). However, the test result may be affected by the concentration of the allergen solution and is less reliable for food allergens because patients may consume the food without a reaction even though skin test to a food shown positive result (Portnoy, 2011). Intracutaneous tests, on the other hand, involve the injection of a dilute extract into the skin and usually use to diagnose drug or sting insect allergy. The intracutaneous test is more sensitive than a skin prick test, which may lead to higher rates of false positive results and could induce a higher risk of systemic reactions (Portnoy, 2011). Overall, the advantage of skin tests is that they are convenient, rapid, sensitive, and inexpensive. The disadvantage of skin tests is that they may associate with some discomfort when performing the test, at risk of inducing a systemic reaction, less pronounced in small children and elderly, and may cause false positive results if the patient has taken antihistamines before the test or complicated by eczema and other skin conditions. Skin tests need to be performed and interpreted by physicians who have been trained. The results of skin tests can vary with the location where the allergens are applied, type of skin prick device, the stability and concentration of the extracts, season and time of day when the tests are performed (Pawankar et al., 2013; Portnoy, 2011; Rusznak & Davies, 1998).

2.2.6.2 *In Vitro* Tests

In vitro tests use an immunoassay to determine the ability of IgE antibodies in a patient's serum to bind to specific allergens in the device. An enzyme-labelled anti-IgE antibody is added to the device, which generates light in varying strengths proportional to the amount of allergen-specific IgE in the patient's serum, measured in units or nanogram per mL (Portnoy, 2011). *In vitro* tests are readily available, able to measure IgE antibodies to multiple allergens in a single blood specimen, does not requires well-trained staff to perform the test, completely safe as it does not involve direct exposure of allergen to the patient, and tests are not affected by any concurrent drug treatment (Birch & Pearson-Shaver, 202; Pawankar et al., 2013; Portnoy, 2011; Rusznak & Davies, 1998). Results of the *in vitro* tests are accurate, reliable and reproducible, and high levels of allergen-specific IgE correlate with a higher probability of true allergy (Chokshi & Sicherer, 2016; Pawankar et al., 2013). Several studies suggested that a high cut-off values for allergen-specific IgE levels may identify the chance of true allergy for some of the common food allergens, namely egg, cow's milk, peanut, and fish with > 95% positive predictive values (PPV) (Chokshi & Sicherer, 2016; Perry, Matsui, Kay Conover-Walker, & Wood, 2004; Portnoy, 2011; Sampson, 2001). The *in vitro* tests may produce a false positive result, whereby a patient with positive tests does not show any symptoms when exposed to the allergen (Portnoy, 2011). Thus, the results of *in vitro* tests should be interpreted with clinical history. The disadvantages of *in vitro* tests include they are more expensive and a longer time is required to obtain the results (Pawankar et al., 2013).

2.2.6.3 Challenge Tests

In oral food challenges to diagnose food allergy, the patient receives increasing doses of the suspected food allergen under the supervision of a trained allergist with proper equipment and medications (Portnoy, 2011). There are three types of oral food challenges, namely, open challenge, single blind challenge, and double-blind, placebo-controlled challenge (DBPCFC) (Christie, 2013). In an open challenge, food is given openly where both the patient and physician know the food being tested. In single blind challenge, the patient is unaware of the food being tested, while in DBPCFC both the patient and physician do not know the food being tested. The DBPCFC is the "gold standard" for accurate diagnosis of food allergy (Assa'ad, 2019). Using a challenge test in large population-based studies is impractical because they are expensive, difficult to perform, can induce severe reactions and anaphylaxis, and only one allergen can be tested at a time (Chokshi & Sicherer, 2016).

2.2.7 Confounding Factors for Allergic Diseases in Children

2.2.7.1 Genetic Factors

Allergic diseases are highly heritable and family history of allergy is the strongest predictor for

allergic diseases (Koplin et al., 2013; Lau, Matricardi, Wahn, Lee, & Keil, 2019). Children with a family history of allergy have a higher risk to develop allergic diseases (50-80%) than those without a family history (20% risk). The risk increases when both parents have allergic diseases (60-80% risk) (Prescott & Tang, 2005). Studies also showed that children with a maternal history of allergic disease are more likely to develop allergic diseases as compared to paternal history (Koplin et al., 2013; Loo et al., 2015; Wu, Chen, & Kuo, 2012). Twin studies have shown that the risks of eczema, allergen sensitisation, and peanut allergy are significantly higher for monozygotic than for dizygotic twins, indicating the strong genetic influence on allergic diseases (Liu et al., 2009; Sicherer et al., 2000; Thomsen et al., 2007). Moreover, findings from genome-wide association studies (GWAS) have identified a large number of loci associated with allergic diseases (Tamari, Tanaka, & Hirota, 2013; Vicente, Revez, & Ferreira, 2017).

2.2.7.2 Environmental Factors

Apart from genetic factors, several environmental factors play a significant role in determining the risk of allergic diseases. The hygiene hypothesis was first proposed by Strachan (1989) when he found an inverse association between number of siblings and hay fever (Strachan, 1989). The hygiene hypothesis suggested that early exposure to microbial components in the environment could reduce the risk of allergic diseases in early childhood (Strachan, 1989). In line with the classical study by Strachan (1989), findings from the China birth cohort (Gao et al., 2019) and the HealthNuts study in Melbourne, Australia (Koplin et al., 2012) demonstrated that children with older siblings were less likely to develop food allergy during the first year of life. It is postulated that increasing number of siblings result in increased microbial contact, which facilitates a Th2-dominant immune response, and subsequently reduce the risk of allergic disease (Koplin et al., 2012).

In addition, living in a farm environment and pet keeping have been identified as important protective factors for childhood allergy. Findings from a cross-sectional study conducted in New Zealand showed that a combination of maternal farm exposure during pregnancy and continued exposure during childhood significantly reduced the risk of eczema in children aged 5-7 years old (Douwes et al., 2008). Maternal exposure to a farming environment enhances the suppressive action of Tregs on Th2 cell differentiation in their offspring, and subsequently reduce the risk of allergic diseases in their offspring (Yu et al., 2018). Meanwhile, findings from two large cross-sectional studies demonstrated that having a dog at home during the first year of life was protective against childhood eczema and food allergy (Ojwang et al., 2019; Koplin et al., 2012). Although studies suggested that increased exposure to microbial stimulation via farm exposure and pet keeping may reduce the risk of childhood allergy, recent studies found that daycare attendance during the first two years of life is associated with a higher risk of allergic diseases in children (Loo et al., 2015; Tokinobu, Yorifuji, Yamakawa, Tsuda, & Doi, 2020). A large prospective cohort study involving 43783 Japanese children showed that daycare attendance at 6-18 months was associated with a higher risk of eczema between ages 1.5-7 years (Tokinobu et al., 2020). Similar findings were found

in the Singapore GUSTO cohort study that children who attended a daycare centre were more likely to develop eczema between 6-12 months of age (Loo et al., 2015).

Antibiotic use may alter host microbiome, thus affects their immune function and subsequent allergy risk (Francino, 2016). Gao et al. (2019) conducted a birth cohort and found that maternal antibiotic use during pregnancy and infant exposure to antibiotic during the first year of life was associated with a higher risk of eczema in Chinese children at 12 months of age. Another cohort study conducted in Japan revealed that antibiotic exposure in children within the first 2 years of life was a risk factor for eczema in children at 5 years of age (Yamamoto-Hanada, Yang, Narita, Saito, & Ohya, 2017). Similar findings were reported by Metsälä and colleagues (2013) in a case-controlled study involving 32474 children in Finland that both maternal and child's use of antibiotics were associated with a higher risk of cow's milk allergy in children.

Caesarean section is another risk factor for allergic diseases in children. A birth cohort conducted by Papathoma and colleagues (2016) in Greece found that children born by caesarean section were more likely to develop food allergy during the first 3 years of life compared to vaginally-born children. Similarly, another nationwide cohort study with 13-year follow-up involving more than 1 million Swedish children showed that caesarean section delivery was associated with an increased risk of food allergy (Mitselou et al., 2018). It has been suggested that children born vaginally are exposed to maternal microbiota from the cervix and vagina which enable them to acquire the normal immunity against allergic diseases (Dominguez-Bello et al., 2010).

Air pollutants originate from both indoor and outdoor environment can have hazardous effects on human health and have shown to be significantly associated with the onset of atopic disease in children (Ahn, 2014). Air pollutants from the indoor environment such as tobacco smoke may affect both innate and adaptive immunity which may indirectly associated with the risk of allergy in children (Qiu et al., 2017). In a study involving 7030 Korean children (6-13 years of age), eczema was significantly associated with maternal smoking during pregnancy and in the first year after birth (Yi et al., 2012). A systematic review of 57 observational studies found that passive smoking significantly increased the risk of eczema and food allergy in children (Saulyte, Regueira, Montes-Martínez, Khudyakov, & Takkouche, 2014). Air pollutants from the outdoor environment include sulphur dioxide, carbon monoxide (CO), and nitrogen dioxide (NO_2) from fuel combustion or emission from motor vehicles (Ahn, 2014). In a Swedish birth cohort involving 2500 children, exposure to air pollution during the first year of life was associated with an increased risk of food sensitisation at 8 years of age (Gruzieva et al., 2012). Findings from a German birth cohort showed that the distance between the residential area to the nearest main road (as a proxy measure for traffic-related pollution) was positively associated with eczema risk in children during the first 6 years of life (Morgenstern et al., 2008).

Limited studies have also suggested that exposure to house dust mites, hot temperature, sex,

ethnicity, birth weight, and pre-term birth might be associated with childhood allergy risk. The Japan birth cohort by Miyake et al. (2007) reported an increased risk of eczema in children exposed to high levels of house dust mites during the first year of life. In a prospective cohort study, Sargen et al. (2014) found that higher temperature was associated with poorly controlled eczema in US children. A large cross-sectional study conducted among 4972 one-year-old infants in Melbourne, Australia found that male sex and East Asian ethnicity was associated with a higher risk of eczema (Martin et al., 2013). The Singapore GUSTO study reported that Indian children had higher odds of eczema as compared to Chinese children during the first 18 months of life (Loo et al., 2015). A meta-analysis including 10 studies suggested that low birth weight (< 2.5 kg) is protective against eczema, while high birth weight (> 4.0 kg) is a risk factor for eczema in children (Panduru, Salavastru, Panduru, & Tiplica, 2014). The Swedish cohort study reported that children with very pre-term birth (< 32 weeks of gestation) were less likely to develop food allergy within the 13-year follow up period (Mitselou et al., 2018).

Overall, studies suggested that exposure to various environmental factors, especially during the 1000 days of life, may influence the risk of allergic diseases in children. Findings from these studies support the importance of interventions targeting the potential modifiable environmental risk factors during this window of opportunity to reduce the risk of childhood allergy.

2.3 Malnutrition

Malnutrition is a universal problem whereby it affects people from different regions around the world at all age groups, sexes, and socioeconomic status (SES) (Development Initiatives, 2018). It is defined as the failure of the body to obtain the appropriate amount of energy and nutrients in order to maintain health and function of the tissues and organ. Malnutrition in the form of wasting, stunting, and underweight can result from an inadequate intake of energy and nutrients while overweight and obesity is a result of excessive intake of energy and nutrients (WHO, 1997). While anyone can be affected by malnutrition, young children are particularly vulnerable to malnutrition. Malnutrition is an important contributor to morbidity and mortality among young children below five years old throughout the world. About 5.9 million children under 5 years of age died in 2015 and almost half (45.0%) of these deaths were attributed to malnutrition (WHO, 2016). Nutritional status of the children can be determined based on four anthropometric indices; namely, length-for-age z-score (LAZ), weight-for-age z-score (WAZ), weight-for-length z-score (WLZ), and BMI-for-age z-score (BAZ). Children are considered as stunted, underweight, or wasted when their z-scores for either of these indices are below two standard deviations from the median value of the reference population, while children with BAZ above two standard deviations are considered as overweight (WHO, 2006).

Over the past few years, the global trend of undernutrition; namely, stunting, underweight, and

wasting are declining in all regions. The global prevalence of stunting and underweight among children under 5 years old have decreased from 26.2% and 16.5% to 21.9% and 13.4% between 2010 and 2018, respectively (Table 2.4). Similarly, the global prevalence of wasting slightly decreased from 7.5% in 2014 to 7.3% in 2018. Although the prevalence of undernutrition showed a decline, a high proportion of undernourished children still found in Africa and Southeast Asia. In contrast, the global trend of overweight has risen slightly in all regions from 5.4% to 5.9% between 2010 and 2018 except for Africa and the Eastern Mediterranean which show a slight decrease. Most of the regions around the world are facing a double burden of malnutrition. Despite the reduction of childhood malnutrition in most of the regions, the progress has been slow and the prevalence of malnutrition across the world remains high, especially in low- and middle-income countries (Development Initiatives, 2018).

Malaysia is one of the low- and middle-income countries facing the double burden of malnutrition, where both undernutrition and obesity coexist. According to the latest National Health and Morbidity Survey (NHMS), the prevalence of stunting, underweight, and wasting in children below five years of age have increased from 17.7%, 12.4%, and 8.0% to 20.7%, 13.7%, and 11.5%, respectively between 2015 and 2016 (IPH, 2016a; UNICEF et al., 2019). In contrast, the prevalence of overweight has reduced from 7.1% to 6.0%. The prevalence of childhood malnutrition is of worrying state and should be given attention as a priority health issue. Continued efforts are needed from all stakeholders including the non-governmental agencies to further improve the nutritional status of Malaysian children especially those under five years of age. Studies should be undertaken to determine the risk factors of childhood malnutrition in Malaysia so that preventive strategies can be taken to cope with this global health issue.

Table 2.4. Global prevalence of malnutrition among children < 5 years old (UNICEF et al., 2014; 2019)

	Stunting		**Underweight**		**Wasting**		**Overweight**	
Region	**2010**	**2018**	**2010**	**2018**	**2014**	**2018**	**2010**	**2018**
Africa	37.1	33.1	19.9	17.1	9.4	7.0	3.9	3.5
Americas	8.2	6.5	2.2	1.6	1.0	0.8	7.0	7.2
South-East Asia	39.4	31.9	31.6	25.6	13.6	15.0	3.1	3.8
Eastern Mediterranean	28.5	24.7	15.1	12.8	9.2	7.8	5.8	5.7
Europe	-	-	-	-	-	-	-	-
Western Pacific	11.1	6.4	4.4	2.5	2.4	2.2	5.8	6.0
Global total	**26.2**	**21.9**	**16.5**	**13.4**	**7.5**	**7.3**	**5.4**	**5.9**

2.3.1 Confounding Factors for Malnutrition in Children

2.3.1.1 Maternal Age

Maternal age is one of the socio-demographic factors that influence the development of malnutrition in children. A study combining five birth cohorts from low- and middle-income countries, namely Brazil, Guatemala, India, the Philippines, and South Africa (n = 19403) found that younger maternal age (≤ 19 years) was associated with a higher risk of stunting in children at 2 years of age, while older maternal age (≥ 35 years) reduced the risk (Fall et al., 2015). Similarly, another study using cross-sectional data from Demographic Health Surveys (DHS) from 18 developing countries (n = 32042) found that children of younger mother (≤ 19 years vs. 20-24 years) were more likely to be stunted by 12-24 months and restricted growth continued after 24 months (Yu, Mason, Crum, Cappa, & Hotchkiss, 2016). A prospective cohort study conducted among 18335 American adults aged 50 years and above demonstrated that their risk of obesity was higher if they were born by their mother at < 25 years or > 35 years compared to those born to mothers aged 25-24 years (Myrskylä & Fenelon, 2012). Overall, studies suggested that children born by mother at a younger age were associated with an increased risk of malnutrition. The inverse association between maternal age and malnutrition in children can be explained by behavioural, social, and biological factors. Younger mothers tend to have lower SES, less educated, and behaviorally immature and therefore might not be able to attend the needs of their children (Fall et al., 2015).

2.3.1.2 Ethnicity

Findings from the Malaysia National Health and Morbidity Survey (NHMS 2016) showed that infants (< 6 months) of Indian mothers were more likely to be wasted compared to Malay mothers (Baharudin et al., 2019). Meanwhile, the prevalence of wasting was significantly lower among children aged 12-23 months from Chinese or other ethnicity compared to Malay ethnicity. For stunting, children aged 12-23 months from Chinese or Indian household had a lower risk of stunting compared to Malay household (Baharudin et al., 2019). Findings from the Health Surveys for England 1998-2009 demonstrated that children of ethnic minority (aged 2-15 years), namely black African and black Caribbean were more likely to be overweight and obese as compared to other 9 ethnic groups (Karlsen, Morris, Kinra, Vallejo-Torres, & Viner, 2014). In a cross-sectional study conducted among children under 5 years of age in China (n = 6570), children of an ethnic minority group were more likely to be stunted compared to their counterparts, but no association was found for overweight (Zhang et al., 2018a). Overall studies suggested that the risk of undernutrition was significantly higher among ethnic minority group, while the association between ethnicity and overnutrition remains inconclusive.

2.3.1.3 Maternal Educational Level

Infants of the mother with primary and secondary educational level were more likely to be wasted compared to mothers with higher educational level, as reported in the NHMS 2016 (Baharudin et al., 2019). A cross-sectional study using Bangladesh DHS 2011 data (n = 7647) showed that children

(aged 0-59 months) born to mothers of higher educational level had a decreased risk of stunting compared to those born to mothers with no education (Sarma et al., 2017). Similar findings were reported in a cross-sectional study using Rwanda DHS 2015 data (n = 3954) that the prevalence of stunting was 2 times higher in children (aged 0-59 months) of mothers with no education compared to mothers with higher education (Nshimyiryo et al., 2019). The association between maternal educational level and stunting in children has also been reported in Bangladesh (Svefors et al., 2018). Svefors et al. (2018) found that the risk of stunting in children at 24 months was significantly higher in children of mother with no education compared to mother who completed primary school in a prospective cohort study. Feng and colleagues (2019) reported that high maternal educational level was associated with a lower risk of underweight but a higher risk of overweight or obesity in children aged 7-18 years old (n = 1081) using data from the China Health Nutrition Survey 2011. Using the prospective data from 11 European cohorts (n = 45413), Ruiz et al. (2016) found that low maternal education is a risk factor for childhood overweight and obesity at 4-7 years of age. Findings from previous studies suggested that high maternal education is protective for childhood undernutrition, but demonstrated a U-shaped association for overnutrition. More studies are needed to determine the influence of maternal education on childhood malnutrition.

2.3.1.4 Maternal Work Status

Findings from the NHMS 2016 suggested that the prevalence of stunting, underweight, and wasting was significantly higher among infants (12-23 months) of unemployed mothers compared to employed mothers (Baharudin et al., 2019). Meanwhile, a cross-sectional study conducted among 149571 Indonesian children under 5 years of age found that children of non-working mothers were more likely to be stunted compared to working mothers (Laksono, Ibad, Mursita, Kusrini, & Wulandari, 2019). A prospective cohort study conducted in the UK (n = 7894) revealed that maternal employment was positively associated with BMI in children at 14 years of age (Fitzsimons & Pongiglione, 2018). In line with Fitzsimons and Pongiglione (2018), Hope and colleagues (2015) reported that maternal full-time employment was associated with an increased risk of overweight in UK children at 7 years of age in a prospective cohort study (n = 9827). Overall, findings from previous studies suggested that maternal non-employment was associated with childhood undernutrition, while full-employment was associated childhood overnutrition. Further studies are needed to assess maternal working duration to further explain the influence of maternal employment on childhood malnutrition.

2.3.1.5 Monthly Household Income

In a cross-sectional study conducted in North Maluku province of Indonesia (n = 2168), children under 5 years of age from the poorest families were more likely to be stunted compared to those from middle income and less poor families (Ramli et al., 2009). A longitudinal birth cohort

conducted across 7 resource-poor settings in Bangladesh, Brazil, India, Nepal, Peru, South Africa, and Tanzania (n = 1197) found that lower SES was associated with an increased risk of stunting at 24 months of age (MAL-ED Network Investigators, 2017). O'Dea and Dibley (2014) found that low and middle SES was significantly associated with obesity in Australian children aged 6-18 years old compared to high SES in a cross-sectional study. Kim and von dem Knesebeck (2018) conducted a systematic review and meta-analysis using 21 cohort studies from the Europe countries and found that the risk of obesity in children and adults were influenced by lower household income. Overall, findings from previous studies suggested that low household income is a risk factor for both under- and overnutrition in children.

2.3.1.6 Gestational Age at Birth

Christian et al. (2013) analysed data from 14 prospective birth cohorts from low- and middle-income countries and found that children born with adequate size for gestational age (AGA) but preterm were more likely to be stunted, wasted, and underweight at 24 months of age compared to those with term AGA. Danaei et al. (2016) analysed data from population-based surveys in 137 developing countries and demonstrated that fetal growth restriction and preterm birth were the major contributing factor towards stunting in children aged 24-35 months. Vasylyeva et al. (2013) extracted data of 160 children and adolescents aged 10-21 years, who born prematurely at $\leq$ 37 weeks of gestations, from pediatric clinics in Amarillo and found that duration of gestational age was positively associated with risk of obesity. In summary, evidence shows that preterm birth is associated with an increased risk of childhood malnutrition.

2.3.1.7 Parity

Findings from a cross-sectional study conducted among 3100 children aged 5-12 years old in Colombia demonstrated that children born to multiparous mothers were more likely to be stunted compared to primiparous mothers (Dekker et al., 2010). Sha et al. (2019) conducted a prospective cohort study among 893 mother-child pairs in Changsha, China and found that multiparity was associated with slower weight-growth velocity in children from 0 to 18 months of age. Consistent with Sha et al. (2019), another prospective cohort study conducted among 9031 mother-child pairs in the Netherlands reported that children of multiparous mothers had a lower risk of overweight at 6 years of age (Gaillard et al., 2014). Overall, findings from previous studies suggested that multiparity is protective against overnutrition, but is a risk factor for undernutrition in children.

2.3.1.8 Pre-pregnancy BMI

A cross-sectional study conducted among 7541 European children (mean age = 4.7 years) showed

that maternal pre-pregnancy overweight or obesity was associated with an increased risk of overweight or obesity in children (Androutsos et al., 2018). Similar findings were reported in a prospective cohort study conducted among 858 Singaporean children maternal pre-pregnancy overweight status was associated with overweight or obesity in children at 48 months of age (Aris et al., 2018). In another prospective cohort including 1744 mother-child pairs in China indicated that maternal pre-pregnancy underweight was associated with a higher risk of underweight in children at a mean age of 8.8 years old (Li et al., 2018). Maternal pre-pregnancy weight status is an important risk factor for childhood malnutrition. Research suggests that pre-pregnancy underweight is associated with undernutrition, while pre-pregnancy overweight or obesity is associated overnutrition in children.

2.3.1.9 Gestational Weight Gain

Androutsos et al. (2018) reported that gestational weight gain exceeding the Institute of Medicine (IOM) recommendations was associated with overweight or obesity in European children at 4.7 years of age (n = 7541) in a cross-sectional study. Results from three combined German cohort studies (n = 6254) showed that excessive gestational weight gain (GWG) was associated with a 28.0% increased risk of overweight in children at age 5-6 years (Beyerlein et al., 2012). A consistent finding was reported by Voerman et al. (2019) in that excessive GWG was associated with higher risks of childhood overweight or obesity (2-18 years of age) using data from 37 birth cohorts from Europe, North America, and Australia (n = 162129). Li et al. (2018) found that average GWG was inversely associated with the risk of underweight in 1744 Chinese children at a mean age of 8.8 years old. While research suggests that excessive GWG is a risk factor for childhood overnutrition, studies assessing the association between maternal GWG and undernutrition are limited and warrant further study.

2.3.1.10 Mode of Delivery

Findings from a prospective cohort study conducted among 6599 infants in New Zealand showed that infants born by planned caesarean section were more likely to become obese at age 24 months but no association was found at 54 months (Masukume et al., 2019). Another cohort study conducted in Ireland (n = 11134) reported that infants delivered by emergency caesarean section were associated with an increased risk of obesity at age 3 years compared to vaginal delivery (Masukume et al., 2018). Meanwhile, a prospective cohort study conducted across 20 sites in Vietnam (n = 1937) demonstrated that both planned and unplanned caesarean section was associated with an increased risk of overweight or obesity in children at age 8 years compared to vaginal delivery (Lavin & Preen, 2018). Findings from two systematic reviews and meta-analyses showed that caesarean section is associated with a higher risk of overweight/obesity in childhood, adolescence, and adulthood (Kuhle, Tong, & Woolcott, 2015; Li, Zhou, & Liu, 2013). Evidence suggests that caesarean section

is an important risk factor for overweight and obesity in the offspring. More studies are needed to explore the association between mode of delivery and childhood undernutrition.

2.3.1.11 Infant's Sex

According to the NHMS 2016, the risk of stunting, underweight, and wasting was significantly higher in male infants aged 12-23 months compared to female infants (Baharudin et al., 2019). Another cross-sectional study using DHS data from 35 sub-Saharan Africa countries (n = 384928) found that male children had a higher risk for stunting than female children under 5 years of age (Yaya, Oladimeji, Odusina, & Bishwajit, 2020). Similar findings were reported by Ali and colleagues (2017) that the male children under 5 years of age were more likely to be stunted, underweight, and wasted as compared to female children in a cross-sectional study (n = 425) conducted at Northern Ghana. Song et al. (2016) analysed data from the Chinese National Survey (n = 1280239) and reported that male children had a higher risk of overweight and obesity as compared to female children aged 7-18 years old. In line with Song et al. (2016), another cross-sectional study conducted among 12811 Chinese children (mean age = 10.6 years old) found indicated that the odds of overweight or obesity were significantly higher in boys compared to girls (Zhang et al., 2018b). In summary, research suggests that the risk of childhood under- and overnutrition was significantly higher in males compared to females.

2.3.1.12 Birth Weight

A case-control study conducted among children under 5 years of age in Terengganu district, Malaysia (n = 274) found that children with low birth weight were 6 times more likely to have malnutrition (either stunting, underweight, or wasting) as compared to their counterparts (Wong, Moy, & Nair, 2014). Aryastami et al. (2017) analysed data from the 2010 Indonesian National Health Survey (n = 3024) and found that infants born with low birth weight were associated with an increased risk of stunting between 12-23 months of age. A prospective cohort study conducted among 210172 infants in China revealed that children with lower birth weight were more likely to develop underweight, while higher birth weight was associated with an increased risk of overweight between 3-6 years of age (Ye et al., 2010). Rito et al. (2019) analysed data from cross-sectional studies conducted in 22 Europe countries (n = 100583) and found that higher birth weight was associated with a higher risk of overweight in children aged 6-9 years old. Overall, evidence suggests that birth weight play an important role in child's growth. It is possible that genetic and environmental influences during pregnancy may influence fetal growth and subsequent risk of malnutrition in childhood.

2.4 Vitamin D

2.4.1 Background

Vitamin D is a fat-soluble secosteroid which exists in two main forms, vitamin D_2 (or ergocalciferol) and vitamin D_3 (or cholecalciferol). Cholecalciferol is formed from 7-dehydrocholesterol when the skin is exposed to the ultraviolet B (UVB) radiation between 290-315 nm from the sunlight (Pérez-López, 2007). The vitamin D levels obtained from the sunlight is mainly determined by seasons, latitude, the duration and timing of exposure, size of exposed body surface area, skin pigmentation, clothing, and the sunscreen use (Engelsen, Brustad, Aksnes, & Lund, 2005; Osmancevic et al., 2015; Tsiaras & Weinstock, 2011). Vitamin D_3 produced in the skin will then bind to the vitamin D-binding protein and is transported to the bloodstream (Zhu & Okamura, 1995). Apart from sunlight, vitamin D can be obtained from foods and supplements. Dietary sources of vitamin D include vitamin D_2 derived from plants such as mushroom and vitamin D_3 derived from animal sources such as oily fish (salmon, sardines and mackerel), egg yolk, cheese, beef liver, and cod liver oil (US Department of Agriculture, 2016). Vitamin D_2 and D_3 obtained through dietary intake and cutaneous synthesis in the presence of sunlight are then transported to the liver and converted to 25-hydroxyvitamin D [25(OH)D] (Christakos, Ajibade, Dhawan, Fechner, & Mady, 2010). 25(OH)D is the main circulating form of vitamin D and is the best indicator of vitamin D level in the body as the amount of vitamin D produced in the skin and obtained from the foods are well-reflected in serum 25(OH)D concentration. (Kennel, Drake, & Hurley, 2010; Zerwekh, 2008). The 25(OH)D is then transported to the kidney and is hydroxylated to the active form, $1,25(OH)_2D$ (Hollis, & Wagner, 2013). $1,25(OH)_2D$ plays an important role in regulating calcium metabolism by increasing intestinal calcium absorption, suppressing parathyroid hormone secretion, and promoting bone mineralization (Christakos et al., 2010; Christakos, Dhawan, Porta, Mady, & Seth, 2011).

2.4.2 Classification of Vitamin D Status

To date, there is still lack of consensus on an optimal vitamin D level. In November 2010, the Institute of Medicine (IOM) released a new vitamin D recommendation based on available evidence of vitamin D on bone health (IOM, 2011). IOM stated that bone health was the only outcome that was causally influenced by vitamin D and evidence on extraskeletal outcomes such as cancer, autoimmune disease, cardiovascular disease, and type 2 diabetes were inconclusive and data from high quality randomised controlled trials were insufficient. IOM recommended that serum 25(OH)D levels of at least 50 nmol/L should be attained for a "sufficient" level of vitamin D and this cut-off meets the needs of 97.5% of the population. They found no evidence of beneficial effects on bone health with a serum 25(OH)D level above 50 nmol/L at a population level. However, these recommendations have received debates from other experts and they suggested that 25(OH)D levels of at least 75nmol/L should be achieved for extraskeletal outcomes apart from bone health (Bischoff-Ferrari, 2014; Bischoff-Ferrari et al., 2006; Holick et al., 2011).

2.4.3 Prevalence of Vitamin D Insufficiency and Deficiency in Pregnancy

Vitamin D insufficiency and deficiency is a global health problem and pregnant women are one of the vulnerable groups for vitamin D insufficiency and deficiency (Fiscaletti et al., 2017). A high prevalence of vitamin D insufficiency and deficiency (< 50 nmol/L) has been reported among pregnant women worldwide (Table 2.5). The prevalence of vitamin D insufficiency and deficiency ranges from 21.0% to 92.0% in the Asia-pacific region, 10.0% to 43.7% in the Americas region, 27.4% to 94.2% in the Europe region, and 55.8% to 81.0% in the Middle East region. Comparison of vitamin D insufficiency and deficiency prevalence data across countries was difficult because pregnant women recruited in previous studies were from different gestational age. Despite being a tropical country located near to the equator and received perennial sunshine, the prevalence of vitamin D insufficiency and deficiency was reported as high as 71.7% in third-trimester Malaysian pregnant women (Lee et al., 2017).

Table 2.5. Prevalence of vitamin D insufficiency and deficiency (< 50 nmol/L) in pregnant women worldwide

Country	Trimester	Sample size (n)	Prevalence (%)	Reference
Asia-Pacific Region				
Australia	2nd	1156	36.0	Wilson et al., 2018
New Zealand	2nd	1644	21.0	Wilson et al., 2018
Japan	1st – 3rd	2030	84.0	Kanatani et al., 2019
China	3rd	708	75.2	Yun et al., 2017
Thailand	3rd	147	34.0	Pratumvinit et al., 2015
Malaysia	3rd	680	71.7	Lee et al., 2017
India	3rd	200	86.0	Arora et al., 2018
Bangladesh	1st – 3rd	140	62.8	Asaduzzaman et al., 2018
Americas Region				
United States	1st	235	10.0	Flood-Nichols et al., 2015
Canada	2nd – 3rd	336	25.0	Li et al., 2011
Brazil	1st – 3rd	520	43.7	Chrisostomo et al., 2018
Europe Region				
United Kingdom	3rd	977	35.0	Crozier et al., 2012
Spain	1st	453	27.4	Rodríguez-Dehli et al., 2015
Belgium	3rd	665	54.9	Vandevijvere et al., 2012
Turkey	3rd	120	94.2	Baki Yildirim & Koşar Can, 2019
Middle East Region				
Iran	1st - 3rd	6127	55.8	Badfar et al., 2017
Saudi Arabia	1st	578	81.0	Al-Musharaf et al., 2018

Vitamin D insufficiency and deficiency during pregnancy could lead to adverse maternal and foetal outcomes. Pregnant women with low vitamin D levels were at a higher risk of preeclampsia (Shibata et al., 2011), gestational diabetes (Zhang et al., 2015), and emergency cesarean section delivery (Scholl, Chen, & Stein, 2012). Meanwhile, the foetus of a mother with vitamin D deficiency was more likely to experience intrauterine growth restriction (van der Pligt et al., 2018), premature birth (Bodnar, Platt, & Simhan, 2015), and low birth weight (Pérez-López et al., 2015). Emerging evidence over the past few years have demonstrated the important role of maternal vitamin D status during pregnancy in foetal programming, leading to several non-skeletal outcomes such as malnutrition and allergic diseases in the offspring. A discussion of these roles will be elaborated further in the following sections.

2.4.4 Metabolism of Vitamin D in Pregnancy

Maternal vitamin D metabolism changes significantly during pregnancy to attain foetal bone mineral accretion. Calcium is transferred from the mother to the foetus through the placenta, mainly during the third trimester of pregnancy, resulting in approximately 25-30 g of calcium accumulated in the foetal skeleton (Specker, 2004). Active transport of calcium from the mother to the foetus leads to the reduction of maternal total serum calcium levels throughout the pregnancy period and high concentration of calcium in the foetus (Brunette, 1988). Extra calcium was obtained during pregnancy through increasing intestinal calcium absorption to compensate for the calcium being transferred to the foetus (Kent et al., 1991). Total serum 1,25(OH)2D concentrations increased by 2-fold during the third trimester of pregnancy to account for the increased intestinal calcium absorption (Ritchie et al., 1998; Specker, 2004). In contrast, maternal 25(OH)D levels appear unchanged during pregnancy (Mulligan, Felton, Riek, & Bernal-Mizrachi, 2010). Maternal 25(OH)D is transferred to the foetus via the placenta, and the 25(OH)D levels in the foetus are directly correlated with maternal levels (Pérez-López, 2007).

2.4.5 Vitamin D in Pregnancy and Allergic Diseases

Findings from previous animal studies and human cell culture studies have identified the role of vitamin D in regulation of the immune system and an indirect link to allergic response through the reduction of Th1 cytokines production, induction of regulatory T cells, suppression of IgE production by B cells, induction of antimicrobial peptides, and increased IL-10 production (Muehleisen & Gallo, 2013; Rueter et al., 2014). There has been growing interest in the influences of maternal vitamin D status during pregnancy on the development of allergic diseases in offspring. During pregnancy, the foetus is entirely dependent on the mother for an adequate supply of 25(OH)D. Previous studies have shown that maternal serum 25(OH)D concentrations during pregnancy is significantly associated with infant cord blood 25(OH)D (Hoxha, Zoto, Deda, & Vyshka, 2014; Novakovic et al., 2012). Inadequate maternal 25(OH)D levels during pregnancy can

affect immune development and predisposition for allergy in infants (Rueter, Siafarikas, Prescott, & Palmer, 2014). Vitamin D in infants which is acquired from mother through the placenta can influence regulatory T cells activation and Th1-Th2 balance in infants, which in turn leads to the development of allergic diseases (Hoxha et al., 2014; Maslova et al., 2013; Rueter et al., 2014).

Considering the high prevalence of vitamin D deficiency among pregnant women, numerous studies have been conducted to evaluate their relationships with allergy risk in children. Table 2.6 summarises the prospective cohort studies that assess maternal serum 25(OH)D levels during pregnancy or in cord blood at birth with eczema and food allergy in the offspring. Overall, findings from the 13 studies were inconsistent. Four studies found negative associations between maternal vitamin D status with risk of eczema and food sensitisation in children (Baiz et al, 2014; Blomberg et al., 2017; Chiu et al., 2015; Jones et al., 2012). Among these four studies, two studies assessed vitamin D status using maternal serum 25(OH)D concentrations during pregnancy and reported that higher maternal vitamin D levels during pregnancy were associated with decreased risk of eczema (Blomberg et al., 2017; Chiu et al., 2014) and food sensitisation (Chiu et al., 2015) in children. The remaining two studies assessed vitamin D status using cord blood 25(OH)D concentrations and found that higher cord blood vitamin D levels were associated with decreased risk of eczema in children (Baiz et al., 2014; Jones et al., 2012). Two studies found positive relationships between maternal vitamin D levels with eczema (Gale, 2008), food allergy, and food sensitisation (Weisse et al., 2013) in children (Table 2.6). The remaining 10 studies found no evidence of associations between maternal vitamin D status and eczema (Blomberg et al., 2017; Boyle et al., 2017; Gazibara et al., 2016; Hannessy et al., 2018; Loo et al., 2019; Weisse et al., 2013, Wills et al., 2013), food allergy (Blomberg et al., 2017; Hannessy et al., 2018), and food sensitisation (Chawes et al., 2014; Hannessy et al., 2018; Jones et al., 2012; Loo et al., 2019; Stelmach et al., 2015) in children.

Findings from these studies remain inclusive and comparison across studies was difficult due to methodologies differences across these studies. Different methods were used to assess maternal vitamin D status [maternal serum 25(OH)D concentrations during pregnancy or cord blood 25(OH)D concentrations] and vitamin D status was reported using different classifications (continuous data, quartiles, IOM cut-offs, or Endocrine Society's cut-offs). For studies that analysed maternal serum 25(OH)D concentrations during pregnancy, serum was collected at different timing of pregnancy (second or third trimester). In addition, allergy outcomes were assessed at different age and method of outcome assessment varied between studies (parental reports, doctor-diagnosed, and UK Working Party Diagnostic Criteria for eczema; parent reports, serum allergen-specific IgE blood test, skin prick test, and oral food challenge for food allergy and food sensitisation). Meanwhile, confounders adjusted in multivariate analysis differed between studies might also be one of the reasons for inconsistent findings in these studies. Due to these limitations, the evidence available is insufficient to provide clinical practice guideline and further studies assessing the effects of vitamin D deficiency during pregnancy on allergy outcomes are needed.

Table 2.6. Relationships between maternal vitamin D status during pregnancy with eczema and food allergy in children

Reference and Study Location	Study design	Subjects	Exposure	Outcomes	Main findings
Gale et al., 2008 Southampton, UK	Prospective cohort study	596 mother-child pairs	Maternal serum 25(OH)D at 3rd trimester of pregnancy [<30 (Ref), 30-50, 50-75, >75 nmol/L]	Eczema (UK WPDC) [measured at 9 months & 9 years]	Higher maternal 25(OH)D level (>75 nmol/L) was associated with increased risk of eczema in children at 9 months.
Weisse et al., 2013 Leipzig, Germany	Prospective cohort study	378 mother-child pairs	Maternal serum 25(OH)D at 3rd trimester of pregnancy [Q1 (15-35), Q2 (36-55), Q3 (55-80), Q4 (80-152) nmol/L] Cord blood 25(OH)D [Q1 (3-17), Q2 (17-27), Q3 (27-43), Q4 (43-100) nmol/L]	Eczema (PP) Food allergy (PP) Food sensitisation (sIgE) [measured at 1 & 2 years]	No association between maternal 25(OH)D and eczema in children. Higher maternal 25(OH)D level was associated with increased risk of food allergy and food sensitisation in children at 2 years. Higher cord blood 25(OH)D level was associated with increased risk of food allergy in children at 2 years.
Wills et al., 2013 South West, England	Prospective cohort study	5513 mother-child pairs	Maternal serum 25(OH)D at 3rd trimester of pregnancy [<38 (Ref), 38-52, 52-67, 67-89, ≥89 nmol/L]	Eczema (PP) [measured at 7.5 years]	No association between maternal 25(OH)D and eczema in children.
Chiu et al., 2015 Keelung, Taiwan	Prospective cohort study	164 mother-child pairs	Maternal serum 25(OH)D at 2nd trimester of pregnancy [<50 (Ref), 50-75, ≥75 nmol/L]	Eczema (DD) Food sensitisation (sIgE) [measured at 6 months, 1, 1.5, 2, 3, & 4 years]	Higher maternal 25(OH)D level (50-75 nmol/L) were associated with decreased risk of eczema in children at age 4 years. Higher maternal 25(OH)D level (≥75 nmol/L) was associated with decreased risk of food sensitisation in children at age 1.5 and 2 years.
Gazibara et al., 2016 Rotterdam, Netherlands	Prospective cohort study	3019 mother-child pairs	Maternal serum 25(OH)D at 2nd trimester of pregnancy Cord blood 25(OH)D [<25, 25-50, 50-75, ≥75 (Ref) nmol/L]	Eczema (PP) [measured at 6 months, 1, 2, 3, & 4 years]	No association between maternal 25(OH)D and eczema in children. No association between cord blood 25(OH)D and eczema in children.
Blomberg et al., 2017 Massachusetts, US	Prospective cohort study	1418 mother-child pairs	Maternal serum 25(OH)D at 2nd trimester of pregnancy Cord blood 25(OH)D [<25, 25-50, 50-75, ≥75 (Ref) nmol/L]	Eczema (PP) [measured between 0-3 years]	Lower maternal 25(OH)D level (<25 nmol/L) was associated with increased risk of eczema in children. No association between cord blood 25(OH)D with eczema in children.

Note: PR: Parent reports; DD: Doctor diagnosed; SPT: Skin prick test; OFC: Oral food challenge; sIgE: serum allergen-specific IgE blood test; UK WPDC: UK Working Party Diagnostic Criteria; Ref: Reference group

Table 2.6. Relationships between maternal vitamin D status during pregnancy with eczema and food allergy in children (continued)

Reference and Study Location	Study design	Subjects	Exposure	Outcomes	Main findings
Boyle et al., 2017 Auckland, New Zealand	Prospective cohort study	922 mother-child pairs	Maternal serum 25(OH)D at 2nd trimester of pregnancy (continuous data)	Eczema (PP) [measured between 5-6 years]	No association between maternal 25(OH)D and eczema in children.
Hennessy et al., 2018 Cork, Ireland	Prospective cohort study	1537 mother-child pairs	Maternal serum 25(OH)D at 2nd trimester of pregnancy (<75, ≥75 nmol/L) Cord blood 25(OH)D (<50, ≥50 nmol/L)	Eczema (UK WPDC) [measured between 6-24 months] Food allergy (SPT, OFC) [measured at 2 years]	No association between maternal 25(OH)D with eczema and food allergy in children. No association between cord blood 25(OH)D with eczema and food allergy in children.
Loo et al., 2019 Singapore	Prospective cohort study	925 mother-child pairs	Maternal serum 25(OH)D at 3rd trimester of pregnancy [<50, 50-75, ≥75 (Ref) nmol/L]	Eczema (PP) Food sensitisation (SPT) [measured at 18 months, 3, & 5 years]	No association between maternal 25(OH)D with eczema and food sensitisation in children.
Baiz et al., 2014 Poitiers & Nancy, France	Prospective cohort study	239 mother-child pairs	Cord blood 25(OH)D (per 5 ng/mL increase)	Eczema (PP) [measured at 1, 3, & 5 years]	Higher cord blood 25(OH)D levels were associated with a decreased risk of eczema in children at aged 1, 3, and 5 years.
Chawes et al., 2014 Copenhagen, Denmark	Prospective cohort study	257 mother-child pair	Cord blood 25(OH)D (<50 vs. ≥75 nmol/L)	Eczema (DD) [measured at 7 years] Food sensitisation (sIgE) [measured between 0-6 years]	No association between cord blood 25(OH)D with eczema and food sensitisation in children.
Jones et al., 2012 Perth, Australia	Prospective cohort study	231 mother-child pairs	Cord blood 25(OH)D [<50, 50-75, ≥75 (Ref) nmol/L]	Eczema (DD, PR) Food sensitisation (PR, SPT) [measured at 12 months]	Lower cord blood 25(OH)D level (<50nmol/L) was associated with increased risk of eczema in children. No association between cord blood 25(OH)D and food sensitisation in children.
Stelmach et al., 2015 Poland	Prospective cohort study	190 mother-child pairs	Cord blood 25(OH)D [below vs. above lower quartile]	Food allergy (PP) [measured at 2 years]	No association between cord blood 25(OH)D and food allergy in children.

Note: PR: Parent reports; DD: Doctor diagnosed; SPT: Skin prick test; OFC: Oral food challenge; sIgE: serum allergen-specific IgE blood test; UK WPDC: UK Working Party Diagnostic Criteria; Ref: Reference group

2.4.6 Vitamin D in Pregnancy and Malnutrition

Apart from allergy diseases, maternal vitamin D status during pregnancy also plays a role in other outcomes such as malnutrition. Maternal vitamin D deficiency during pregnancy has negative impacts on bone development during foetal growth which may be sustained to affect later stature (Viljakainen et al., 2010; Weiler et al., 2005). Besides, there is evidence from cell culture and animal model studies that adipose tissue has both the vitamin D receptor and the ability to synthesize 1,25(OH)D. Foetal vitamin D which is obtained from the mother through the placenta may exert programming effect on foetal adipogenesis, influencing the number of adipocytes in the foetus and subsequent risk of overweight and obesity in the offspring (Lecoutre & Breton, 2015; Morales et al., 2015). The link between maternal vitamin D status during pregnancy and child growth has been assessed in several large birth cohorts; however, results from previous studies have been controversial.

As shown in Table 2.7, five previous studies found an inverse association between maternal 25(OH)D concentrations during pregnancy with body weight and length standard deviation scores (SDS) (Leffelaar, et al., 2010), BMI SDS (Daraki et al., 2018), LAZ (Hanieh et al., 2014), odds of stunting (Toko et al., 2016), and being overweight (Morales et al., 2015) in children. In contrast, only two studies found a positive association between maternal vitamin D concentrations during pregnancy with birth weight, length SDS, BAZ, WAZ, and LAZ in their offspring during early infancy (Eckhardt et al., 2015; Leffelaar, et al., 2010). The remaining eight studies found no significant associations between maternal 25(OH)D status and child growth (Boyle et al., 2017; Chi et al., 2018; Gale et al., 2008; Gould et al., 2017; Krishnaveni et al., 2011; Miliku et al., 2019; Ong et al., 2016; van Eijsden et al., 2013). Differences in timing of serum 25(OH)D collection during pregnancy, classifications of vitamin D status, and child growth outcomes being studied may explain for the discrepancy in findings across studies. More studies are needed to identify the role of maternal vitamin D status on child growth, especially in developing countries where the double burden of malnutrition is on the rise.

2.5 Infant Feeding Practices

2.5.1 Background

Optimal nutrition during the first year of life is critical to ensure healthy growth and development in infants and breastfeeding is a key component during this critical period. Breast milk is the ideal food for infants during the first six months of life as it provides the right amount of nutrients that meet the infant needs (Michaelsen, Weaver, Branca, & Robertson, 2003). The amount of nutrient and energy required by the infants starts to exceed those provided in the breast milk around 6 months of age and complementary foods should be added to fulfil their needs (WHO, 2018). Before 2001, the WHO recommended that the exclusive breastfeeding period for infants should be 4-6 months,

Table 2.7. Relationships between maternal vitamin D status during pregnancy and nutritional status in children

Reference and Study Location	Study design	Subjects	Exposure	Outcomes	Main findings
Gale et al., 2008 Southampton, UK	Prospective cohort study	596 mother-child pairs	Maternal serum 25(OH)D at 3rd trimester of pregnancy [<30 (Ref), 30-50, 50-75, >75 nmol/L]	Weight, length, BMI (measured at birth, 9 months, and 9 years)	No association between maternal 25(OH)D and child growth.
Leffelaar, et al., 2010 Amsterdam, Netherlands	Prospective cohort study	3730 mother-child pairs	Maternal serum 25(OH)D at median 13 weeks of gestation [<30, 30-50, ≥50 (Ref) nmol/L]	Weight SDS, length SDS (measured at birth, 1, 3, 6, 9, and 12 months)	Lower maternal 25(OH)D (<30 mol/L) level was associated with lower birth weight, lower length SDS at 1-month, higher weight SDS at 6 and 9 months, and higher length SDS at 12 months, respectively.
Krishnaveni et al., 2011 Mysore, India	Prospective cohort study	568 mother-child pairs	Maternal serum 25(OH)D between 28-32 weeks of gestation (continuous data)	Height, BMI (measured at 5 and 9.5 years)	No association between maternal 25(OH)D and child growth.
van Eijsden et al., 2013 Amsterdam, Netherlands	Prospective cohort study	1208 mother-child pairs	Maternal serum 25(OH)D at median 13 weeks of gestation	Height (measured between 5-6 years)	No association between maternal 25(OH)D and linear growth in children.
Hanieh et al., 2014 Ha Nam, Vietnam	Prospective cohort study	960 mother-child pairs	Maternal serum 25(OH)D at 32 weeks of gestation (continuous data)	Weight, length, LAZ, stunting (measured at 6 months)	Higher maternal 25(OH)D levels were associated with lower LAZ in infants. No association between maternal 25(OH)D with weight, length, and stunting in children.
Eckhardt et al., 2015 US	Prospective cohort study	2473 mother-child pairs	Maternal serum 25(OH)D ≤ 26 weeks of gestation [<30 (Ref) vs. ≥30 nmol/L]	LAZ, WAZ, BAZ (measured at birth and 4, 8 and 12 months)	Higher maternal 25(OH)D level (≥30 nmol/L) was associated with increased BAZ in infants at birth, increased WAZ at birth and 4 months, and increased LAZ at 12 months, respectively.
Morales et al., 2015 Spain	Prospective cohort study	2358 mother-child pairs	Maternal serum 25(OH)D between 13-15 weeks of gestation [<50, 50-75, ≥75 (Ref) nmol/L]	BAZ, overweight (measured at 1 and 4 years)	Lower maternal 25(OH)D level (<50 nmol/L) was associated with increased risk of overweight in children at one year of age.
Ong et al., 2016 Singapore	Prospective cohort study	910 mother-child pairs	Maternal serum 25(OH)D between 26-28 weeks of gestation [<50, 50-75, ≥75 (Ref) nmol/L]	WAZ. LAZ, BAZ (measured at birth, 3, 6, 9, 12, 15, 18, and 24 months)	No association between maternal 25(OH)D and child growth.

Note: BMI: Body mass index; LAZ: length-for-age z scores; WAZ: weight-for-age z scores; BAZ: BMI-for-age z scores, SDS: standard deviation score

Table 2.7. Relationships between maternal vitamin D status during pregnancy and nutritional status in children (continued)

Reference and Study Location	Study design	Subjects	Exposure	Outcomes	Main findings
Toko et al., 2016 Chulaimbo, Kenya	Prospective cohort study	63 mother-child pairs	Maternal serum 25(OH)D < 26 weeks of gestation [<50 vs. ≥50 (Ref) nmol/L]	Underweight, stunting, wasting (measured at birth)	Lower maternal 25(OH)D level (<50 nmol/L) was associated with increased risk of stunting at birth.
Boyle et al., 2017 Auckland, New Zealand	Prospective cohort study	922 mother-child pairs	Maternal serum 25(OH)D at 15 weeks of gestation (continuous data)	BAZ (measured between 5-6 years)	No association between maternal 25(OH)D and BAZ in children.
Gould et al., 2017 Australia	Prospective cohort study	337 mother-child pairs	Cord blood 25 (OH)D [<25 (Ref), 25-50, ≥50 nmol/L]	WAZ, LAZ (measured at birth, 18 months, and 4 years)	No association between maternal 25(OH)D and child growth.
Daraki et al., 2018 Crete, Greece	Prospective cohort study	532 mother-child pairs	Maternal serum 25(OH)D at median 14 weeks of gestation (continuous data) [<37.7 vs. ≥37.7 (Ref) nmol/L)	BMI SDS (measured at 4 and 6 years)	Lower maternal 25(OH)D level (<37.7 nmol/L) was associated with higher BMI SDS in children at 4 and 6 years of age.
Chi et al., 2018 Wenzhou, China	Prospective cohort study	160 mother-child pairs	Maternal serum 25(OH)D at 3rd trimester of pregnancy [<50 vs. ≥50 (Ref) nmol/L]	Weight and length gained from birth to six months	No association between maternal 25(OH)D with weight and length gained in children from birth to six months.
Miliku et al., 2019 Rotterdam, Netherlands	Prospective cohort study	4903 mother-child pairs	Maternal serum 25(OH)D between 18-23 weeks of gestation Cord blood 25(OH)D [<25.0, 25-50, 50-75, ≥75 (Ref) nmol/L]	BMI (measured at 6 years)	No association between maternal and cord blood 25(OH)D with BMI in children.

Note: BMI: Body mass index; LAZ: length-for-age z scores; WAZ: weight-for-age z scores; BAZ: MNI-for-age z scores, SDS: standard deviation score

followed by the introduction of complementary foods thereafter (WHO, 1995a). This feeding guideline has been revised in 2001 based on a systematic review and expert consultation, and infants are now recommended to be exclusively breastfed for the first 6 months of life and complementary foods should be introduced at 6 months along with continued breastfeeding until 2 years of age or beyond (WHO, 2001).

Globally, just above two in five (42%) of the infants less than 6 months of age were exclusively breastfed and 65% of these were continually breastfed until 2 years of age (Table 2.8). Above two-third (69%) of infants were introduced with complementary foods between 6-8 months of age and a low rate (29%) of infants between 6-23 months received the minimum number of food groups (UNICEF, 2019). The prevalence of infant and young child feeding practices varied across regions. The rates of exclusive breastfeeding range from 30% in East Asia and the Pacific, as well as the Middle East and North Africa to 55% in Eastern and Southern Africa. In terms of introduction of complementary feeding between 6-8 months, the prevalence ranges from 52% in South Asia to 84% in Latin America and the Caribbean, as well as East Asia and the Pacific. In terms of minimum diet diversity, the proportions of children who received the minimum number of food groups in Latin America and the Caribbean (60%) were almost triple that in South Asia (20%). About 4 in 5 children were continually breastfed at 12-23 months compared to only 1 in 8 children in North America. In Malaysia, the latest National Health and Morbidity Survey (IPH, 2016a) reported that 47.1% of the children less than six months were exclusively breastfed, 39.4% were continually breastfed until two years old, and 66.4% received at least four food groups per day. Information on the prevalence of complementary food introduction was not available.

Table 2.8. Global rates of infant and young child feeding practices (UNICEF, 2019)

Region	Exclusive breastfeeding (0-5 months) (%)	Introduction of complementary foods (6-8 months) (%)	Minimum diet diversity (6-24 months) (%)	Continued breastfeeding (12-23 months) (%)
Eastern and Southern Africa	55	77	24	72
South Asia	54	52	20	78
Latin America & the Caribbean	38	84	60	45
North America	35	No data	No data	13
West & Central Africa	34	68	25	64
Eastern Europe & Central Asia	33	75	No data	47
East Asia & the Pacific	30	84	40	60
Middle East & North Africa	30	78	36	47
Global total	**42**	**69**	**29**	**65**

Overall, a high number of children still do not comply with WHO infant feeding recommendations. The complementary feeding period is a critical period for rapid growth and development. Inappropriate nutrition during this critical period may lead to increased risk of adverse health outcomes including malnutrition and allergic diseases. The effects of infant feeding practices on the development of childhood allergy and malnutrition will be discussed in the following sections.

2.5.2 Infant Feeding Practices and Allergic Diseases

The immunomodulatory components in breast milk such as IgA, cytokines, chemokines, growth factors, and essential fatty acids are essential to promote development of the immune system in infants (Böttcher, Fredriksson, Hellquist, & Jenmalm, 2003; Böttcher, Jenmalm, Garofalo, & Björkstén, 2000; Snijders et al., 2006). Th1-type cytokines such as TGF-β, IL-12 and the soluble form of CD14 (sCD14) are found abundantly in the breast milk and play an important role in determining the Th1-Th2 balance, and subsequently the development of allergic diseases (Camporota, 2001; Jones et al., 2002; Oddy et al., 2003; Saito, Yoshida, Ichijo, Ishizaka, & Tsujii, 1993). Besides, breastfeeding promotes the establishment of the intestinal flora predominantly by Bifidobacteria and Lactobacillus and stimulate a Th1 response which protects infants against allergy (Walker & Iyengar, 2014).

Despite the beneficial role of breast milk on childhood allergy, inconsistent findings have been reported in previous studies (Table 2.9). While most studies found no association between breastfeeding duration and risk of eczema and allergy (Bion et al., 2016; Goldsmith et al., 2016; Jelding-Dannemand et al., 2015; Laubereau et al., 2005; Turati et al., 2016; Wang et al., 2017), three studies found that prolonged breastfeeding may be a risk factor for eczema and food allergy in children (Alkazemi et al., 2018; Matsumoto et al., 2019; Taylor-Robinson et al., 2016). Systematic reviews and meta-analysis by pooling 27 prospective cohort studies found no evidence of association between breastfeeding and eczema risk in children (Lin et al., 2019; Yang et al., 2009). Reduced risk of eczema below two years of age was found among children who were exclusively breastfed for 3-4 months compared to those who were breastfed for less than 3-4 months, while no association was found for food allergy risk based on a systematic review and meta-analysis conducted by Lodge et al. (2015).

Apart from breastfeeding, age at introduction of complementary feeding also play an important role in the development of allergic diseases in children. According to the hygiene hypothesis, lack of early childhood exposure to infectious agents and bacterial infections might increase child's susceptibility to allergic diseases by suppressing the natural development of the immune system (Strachan, 1989). Early introduction to allergenic foods might decrease the risk of atopic disease by promoting tolerance through regulatory T-cell (Treg) pathways and minimize the chance of sensitisation through the skin (Chin, Chan, & Goldman, 2014; Lack, 2008). In other words, without a proper trigger of the Treg pathway by the introduction of allergenic foods during early life, it will become underused and ineffective in suppressing inappropriate allergen-specific T cell response leading to the development of allergic diseases.

The protective effects of early introduction of allergenic foods against food allergy have been reported in two randomised controlled trials (Du Toit et al., 2015; Perkin et al., 2016) (Table 2.9). Du Toit et al. (2015) found that high-risk children between 4-11 months of age who were introduced to peanuts had a lower risk of peanut allergy at five years of age compared to those who avoided

Table 2.9. Relationships between infant feeding practices with eczema and food allergy in children

Reference and Study Location	Study design	Subjects	Exposure	Outcomes	Main findings
Duration of breastfeeding					
Goldsmith et al., 2016 Melbourne, Australia	Cross-sectional	4537 mother-child pairs	Duration of exclusive breastfeeding [0(Ref), 1, 2, 3, 4, 5, 6 months]	Food allergy (SPT, OFC) [measured at 12 months]	No association between duration of breastfeeding and food allergy in children.
Laubereau et al., 2005 Munich & Wesel, Germany	Prospective cohort study	3903 mother-child pairs	Duration of exclusive breastfeeding [<4 (Ref) vs. ≥4 months]	Eczema (PR, DD) [measured at 3 years]	No association between duration of breastfeeding and eczema in children.
Jelding-Dannemand et al., 2015 Copenhagen, Denmark	Prospective cohort study	335 mother-child pairs	Duration of exclusive breastfeeding [continuous data]	Eczema (DD) Food sensitisation (SPT, sIgE) [measured at 0.5, 1.5, 4, 6, and 7 years]	No association between duration of exclusive breastfeeding with eczema and food sensitisation in children.
Bion et al., 2016 Isle of Wight, England	Prospective cohort study	1456 mother-child pairs	Duration of breastfeeding [0(Ref), 1-6, >6 months] Duration of exclusive breastfeeding [0(Ref), 1-4, >4 months]	Eczema (PR) [measured at 10 and 18 years]	No association between duration of breastfeeding and eczema in children.
Taylor-Robinson et al., 2016 (UK)	Prospective cohort study	14499 mother-child pairs	Duration of breastfeeding [0(Ref), ≤1 week, 1-6 weeks, 6 weeks - 6 months, >6 months]	Eczema (PR) [measured at 5 years]	Breastfeeding for 1–6 weeks and ≥6 months were associated with increased risk of eczema in children.
Wang et al., 2017 Leicestershire, UK	Prospective cohort study	5676 mother-child pairs	Duration of breastfeeding [0(Ref), 1-3, 4-6, >6 months]	Eczema (PR) [measured from age 1-17 years]	No association between duration of breastfeeding and eczema in children.
Turati et al., 2016 Northern & Central Italy	Case-control study	451 cases, 451 control	Duration of breastfeeding [exclusive breastfeeding (Ref) vs. partial breastfeeding at 5 months]	Eczema (PR, DD) [measured between 3-24 months]	No association between duration of breastfeeding and eczema in children.
Alkazemi et al., 2018 Kuwait	Case-control study	100 cases, 100 control	Duration of exclusive breastfeeding [<6(Ref) vs. ≥6 months]	Food allergy (DD, SPT, sIgE) [measured between 0-13 years]	Exclusive breastfeeding for ≥6 months was associated with increased risk of food allergy in children.
Matsumoto et al., 2019 Japan	Retrospective cohort study	46616 mother-child pairs	Duration of breastfeeding [0 (Ref), partial breastfeeding <1, 1-2, 3-5, and 6-7 months, exclusive breastfeeding to 6-7 months]	Food allergy, eczema (PP) [measured at between 6-18 months and 6-66 months]	Exclusive breastfeeding for 6-7 months was associated with increased risk of food allergy in children. Partial breastfeeding for <6 months was associated with decreased risk of food allergy in children with eczema.

Note: PR: Parent reports; DD: Doctor diagnosed; SPT: Skin prick test; OFC: Oral food challenge; sIgE: serum allergen-specific IgE blood test; Ref: Reference group

Table 2.9. Relationships between infant feeding practices with eczema and food allergy in children (continued)

Reference and Study Location	Study design	Subjects	Exposure	Outcomes	Main findings
Yang et al., 2009	Systematic review and meta-analysis of 27 prospective cohort studies		Duration of exclusive breastfeeding (different definition across studies)	Eczema (PR, DD)	No strong evidence of a protective effect of exclusive breastfeeding on eczema risk.
Lodge et al., 2015	Systematic review and meta-analysis Eczema: 24 cohort, 17 cross-sectional, 1 case-control study Food allergy: 9 cohort, 4 cross-sectional studies		Duration of breastfeeding [<3-4 (Ref) vs. ≥3-4]	Eczema (PR, DD, Records) [<2 vs. ≥2 years] Food allergy (PR, DD, Records, sIgE, SPT, ORC) [<5 vs. ≥5 years]	Exclusive breastfeeding for 3-4 months was associated with decreased risk of eczema in children ≤ 2 years of age. No association was found between breastfeeding duration and food allergy in children.
Lin et al., 2019	Systematic review and meta-analysis of 27 prospective cohort studies		Duration of exclusive breastfeeding / total breastfeeding (different definition across studies)	Eczema (PR, DD)	No association between duration of exclusive breastfeeding or total breastfeeding with eczema risk. However, significant effects were found when atopic heredity was taken into account. Longer exclusive breastfeeding duration was protective against eczema in cohorts with atopic heredity, while it became a risk factor in cohorts without atopic heredity.
Age at introduction of complementary feeding					
Koplin et al., 2010 Melbourne, Australia	Cross-sectional	2589 mother-child pairs	Ages at introduction of egg [4-6 (Ref), 7-9, 10-12, >12 months] Ages at introduction of solids [<4 (Ref), 4, 5, 6, >6 months]	Egg allergy (SPT, OFC) [measured at 12 months]	Late introduction of egg into the diet (≥ 10 months) was associated with higher risk of egg allergy in children at 12 months. No association between age at introduction of solids and development egg allergy in children.
Turati et al., 2016 Northern & Central Italy	Case-control study	451 cases, 451 control	Age at introduction of solids [exclusive breastfeeding (Ref) vs. weaning at 4 & 5 months]	Eczema (PR, DD) [measured between 3-24 months]	Introduction of solid foods at 4 or 5 months was associated with lower risk of eczema in children.
Alkazemi et al., 2018 Kuwait	Case-control study	100 children with food allergy, 100 control	Age at introduction of complementary feedings [<6 (Ref) vs. ≥6 months]	Food allergy (DD, SPT, sIgE) [measured between 0-13 years]	No association between age at introduction of complementary feedings and development food allergy in children.

Note: PR: Parent reports; DD: Doctor diagnosed; SPT: Skin prick test; OFC: Oral food challenge; sIgE: serum allergen-specific IgE blood test; Ref: Reference group

Table 2.9. Relationships between infant feeding practices with eczema and food allergy in children (continued)

Reference and Study Location	Study design	Subjects	Exposure	Outcomes	Main findings
Taylor-Robinson et al., 2016 (UK)	Prospective cohort study	14499 mother-child pairs	Age at introduction of solids [<4 vs. ≥4 (Ref) months] Age at introduction of cow's milk [<9 vs. ≥9 (Ref) months]	Eczema (PR) [measured at 5 years]	Early introduction of solids (<4 months) and cow's milk under 9 months were associated with an increased risk of eczema in children.
Elbert et al., 2017 Rotterdam, Netherlands	Prospective cohort study	5202 mother-child pairs	Age at introduction of allergenic foods [≤6 vs. ≥6 months]	Eczema (PR, DD) Food allergy (PR, DD) Food sensitisation (SPT) [measured at 10 years]	No association between timing of allergenic food introduction with eczema, food allergy, and sensitisation in children.
Tham et al., 2018 Singapore	Prospective cohort study	1152 mother-child pairs	Age at introduction of allergenic foods [<10 vs. ≥10 months]	Food allergy (SPT) [measured at 18 and 36 months]	No association between timing of introduction of allergenic foods and development of food allergy in children.
Thorisdottir et al., 2019 Iceland	Prospective cohort study	144 mother-child pairs	Age at introduction of solids [measured at 1, 2, 3, 4, 5, and 6 months (yes vs. no)]	Food sensitisation (sIgE) [measured at 6 years]	Early introduction of solid (≤4 months) increased the risk of food sensitisation in children.
Gao et al., 2019 Changsha, China	Prospective cohort study	903 mother-child pairs	Age at introduction of solid food [<6 vs. ≥6 (Ref) months]	Eczema and food allergy [measured at birth, 1, 3, 6, 8, and 12 months]	Solid food introduction below six months was associated with increased risk of food allergy in children during the first year of life. No association was found between age of solid food introduction and eczema.
Du Toit et al., 2015 London, UK	Randomised, controlled trial	640 high risk infants aged 4-11 months with eczema and /milk allergy	Peanut protein consumption by the exposed group.	Peanut allergy (sIgE, SPT, OFC) [measured at 5 years]	Allergic infants who consumed peanut-based products had a much lower incidence of peanut allergy at five years compared to those who avoid peanut consumption.
Perkin et al., 2016 London, UK	Randomised, controlled trial	1303 exclusively breastfed infants aged 3 months	Sequential introduction of 6 allergenic foods to the exposed group starting from age 3 months to 6 months vs. exclusive breastfeeding ≥6 months	Food allergy (SPT, OFC [measured at 1 and 3 years]	Early introduction of allergenic foods showed a significant reduction in the incidence of food allergy in children compared to those who were exclusively breastfed until six months.
Waidyatillake et al., 2018	Systematic review and meta-analysis of 2 randomised controlled trials, 11 cohort, 2 case-control, 1 cross-sectional study		Age at introduction of solid food	Eczema	Age at introduction of solid foods was not associated with eczema. There is no sufficient evidence to identify the best timing for solid food introduction whether at 4 months, 4-6 months, or >6months in prevention of eczema risk.

Note: PR: Parent reports; DD: Doctor diagnosed; SPT: Skin prick test; OFC: Oral food challenge; sIgE: serum allergen-specific IgE blood test; Ref: Reference group

Table 2.9. Relationships between infant feeding practices with eczema and food allergy in children (continued)

Reference and Study Location	Study design	Subjects	Exposure	Outcomes	Main findings
Diet diversity					
Turati et al., 2016 Northern & Central Italy	Case-control study	451 cases, 451 control	Diet diversity at 4 months [0 (Ref), 1-2, 3-22 food groups] Diet diversity at 5 months [0 (Ref), 1-7, 8-22 food groups]	Eczema (PR, DD) [measured between 3-24 months]	Introduction of a high number of different solid foods at 4 (3-22 food groups) or 5 months (8-22 food groups) was associated with lower risk of eczema in children.
Filipiak et al., 2007 Munich & Wesel, Germany	Prospective cohort study	4753 mother-child pairs	Diet diversity at 4 months [0 (Ref), 1-2, 3-8 food groups] Diet diversity at 6 months [0 (Ref), 1-2, 3-4, 5-8 food groups]	Eczema (DD) [measured at 4 years]	No association between diet diversity at 4 and 5 months with eczema risk in children.
Zutavern et al., 2008 Germany	Prospective cohort study	2073 mother-child pairs	Diet diversity at 4 months [0 (Ref), 1-2, 3-8 food groups]	Eczema (PR, DD) [measured at 6 years]	No association between diet diversity at 4 months with eczema risk in children. However, in children without early skin or allergic symptoms, introduction of a more diverse diet (3-8 food groups) was associated with higher eczema risk.
Roduit et al., 2012 Austria, Finland, France, Germany, Switzerland	Prospective cohort study	1041 mother-child pairs	Diet diversity between 3-12 months [0-3, 4-5, 6 (Ref) food groups]	Eczema (PR, DD) [measured at 1 year]	Introduction of less diverse food groups (<6 food groups) was associated with increased risk of eczema in children.
Roduit et al., 2014 Austria, Finland, France, Germany, Switzerland	Prospective cohort study	856 mother-child-pairs	Diet diversity from 3-12 months [0-3, 4-5, 6 (Ref) food groups]	Food allergy (PR, DD) [measured at 6 years]	Introduction of less diverse food groups (<6 food groups) was associated with increased risk of food allergy in children.
				Food sensitisation (sIgE) [measured at 4.5 and 6 years]	Introduction of less diverse food groups (0-3 food groups) was associated with increased risk of food sensitisation in children.
Nwaru et al., 2014 Finland	Prospective cohort study	3142 mother-child pairs	Food diversity at 3, 4, 6, and 12 months [6 months: 0-4, 5-6, 7-8, >8 (Ref)]	Eczema (PR) [measured at age 5 years]	Introduction of 5-8 different foods at 6 months was marginally associated with higher risk eczema in children.
Elbert et al., 2017 Rotterdam, Netherlands	Prospective cohort study	5202 mother-child pairs	Diversity of allergenic foods at 6 and 12 months [0 (Ref), 1, 2, ≥3 foods]	Eczema (PR, DD) Food allergy (PR, DD) Allergic sensitisation (SPT) [measured at 10 years]	No association between diversity of allergenic foods introduction with allergic sensitisation, food allergy or eczema in children.

Note: PR: Parent reports; DD: Doctor diagnosed; SPT: Skin prick test; OFC: Oral food challenge; sIgE: serum allergen-specific IgE blood test; Ref: Reference group

peanuts. Another study by Perkin et al. (2016) showed that early introduction of allergenic foods between 3-6 months was associated with decreased risk of food allergy in children compared to those who were exclusively breastfed until 6 months. Findings from previous studies suggested that early introduction of complementary foods at ≤ 4 months (Taylor-Robinson et al., 2016; Thorisdottir et al., 2019) and less than six months (Gao et al., 2019) or late introduction of allergenic foods at ≥ 10 months were associated with increased risk of food allergy, food sensitisation, and eczema in children. While Turati et al. (2016) found that introduction of complementary foods at 4-5 months reduced the risk of eczema in children, others have found no evidence on the best timing of complementary feeding on eczema and food allergy risk (Alkazemi et al., 2018; Elbert et al., 2017; Tham et al., 2018; Waidyatillake et al., 2018).

Introduction to a high diversity of food antigens during the complementary feeding period could increase the maturation of the mucosal immune system and oral tolerance, which is indirectly linked to the risk of allergy development (Prescott et al., 2008). Findings from previous studies (Table 2.9) documented that infants who received a less diverse diet at ≤ 6 months of age had a higher risk of food allergy and eczema in later life (Nwaru et al., 2014; Roduit et al., 2012; 2014; Turati et al., 2016). Contradictory findings were reported in high-risk infants, whereby the introduction of a more diverse food was associated with a higher risk of eczema (Zutavern et al., 2008). Filipiak et al. (2007) and Elbert et al. (2017) found no association between diet diversity and risk of allergy in children.

Overall, findings from previous studies on the association between infant feeding practices and the development of allergic diseases in children were inconclusive. Findings from previous studies need to be interpreted with caution as significant findings in the randomised controlled trial was conducted in high-risk infants and the important confounding factors such as family history of allergy were not adjusted in the analysis. Methodology differences such as different age group of study subjects, study design, cut-offs for breastfeeding duration, timing of introduction of complementary feeding, and minimum diet diversity, methods to diagnose allergic diseases, recall bias in reporting infant feeding practices by the parents, and reverse causation effects between feeding practices and allergy should be taken into account when interpreting the findings.

Different complementary feeding recommendations have been implemented across countries (Table 2.10). In Malaysia, the complementary feeding guideline (NCCFN, 2013) is similar to WHO recommendations (WHO, 2003) that complementary foods should be introduced to infants at 6 months onwards, while the Malaysian Society of Allergy and Immunology recommend that allergenic food be introduced between 4-6 months after some complementary foods have been fed and tolerated by the infants (MSAI, 2014). American, Australian, and European allergy expert committee guidelines recommend that complementary foods should be introduced to the infants between 4-6 months of age, while the recommendation on timing of allergenic food introduction was different across countries (ASCIA, 2016; Fewtrell et al., 2017; Greer et al., 2019; Kleinman, 2000; Muraro et al., 2014). The different recommendations may be attributed to differences in the

results of randomised controlled trials on allergenic food consumption, prevalence of peanut allergy, and peanut consumption across countries (Caffarelli et al., 2018). More research is needed to identify the relationships between infant feeding practices and allergy risk so that findings from the research can serve as a reference to improve current infant feeding guidelines for allergy prevention in children.

Table 2.10: Recommendations on timing of complementary food introduction for allergy prevention

Organisation	Timing of Complementary Food (CF) Introduction
World Health Organization (WHO, 2003)	• CF: 6 months onwards. • Allergenic food: No specific recommendations.
Malaysia Dietary Guideline (NCCFN, 2013)	• CF: 6 months onwards. • Allergenic food: No specific recommendations.
Malaysian Society of Allergy and Immunology (MSAI) (MSAI, 2014)	• CF: Between 4-6 months. • Allergenic food: Between 4-6 months after some CF have been fed and tolerated
American Academy of Pediatrics (AAP) (Greer et al., 2019; Kleinman, 2000)	• CF: At 4-6 months of age. • Allergenic food: At 4-6 months
Australasian Society of Clinical Immunology and Allergy (ASCIA) (ASCIA, 2016)	• CF: At around 6 months, but not before 4 months. • Allergenic food: Should be introduced in the first year of life.
European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) (Fewtrell et al., 2017)	• CF: Not be introduced before 4 months but should not be delayed beyond 6 months. • Allergenic food: Any time after 4 months. • Peanut: Between 4 and 11 months for infants at high risk of peanut allergy
European Academy of Allergy and Clinical Immunology (EAACI) (Muraro et al., 2014)	• CF: After 4 months.

2.5.3 Infant Feeding Practices and Malnutrition

While the global prevalence of malnutrition remains high among under 5 years old children, especially in low- and middle-income countries, infant and young child feeding is a key component to promote healthy growth and development in children during the critical period of first 1000 days of life. Previous studies (Table 2.11) demonstrated that longer duration of exclusive or partial breastfeeding was associated with lower risk of overweight and obesity (Horta &Victoria, 2013), higher risk of wasting and stunting (Irarrázaval et al., 2018), lower LAZ (Budree et al., 2017), lower

Table 2.11. Relationships between infant feeding practices and nutritional status in children

Reference and Study Location	Study design	Subjects	Exposure	Outcomes	Main findings
Duration of breastfeeding					
Campbell et al., 2018 Bhutan	Cross-sectional	441 children <24 months	Exclusive breastfeeding Predominant breastfeeding under 6 months (yes vs. no)	Stunting (LAZ<-2) Underweight (WAZ<-2), Wasting (WLZ<-2) Overweight (WLZ>2)	No association between exclusive breastfeeding and undernutrition in children. Exclusive and predominant breastfeeding under 6 months were associated with reduced risk of overweight.
Irarrázaval et al., 2018 Haiti	Cross-sectional	278 children <24 months	Exclusive breastfeeding at 6 months Predominant breastfeeding under 6 months (yes vs. no)	Stunting (LAZ<-2) Underweight (WAZ<-2), Wasting (WLZ<-2)	Exclusive breastfeeding at 6 months was associated wasting and underweight. Predominant breastfeeding under 6 months was associated with underweight and stunting.
Seach et al., 2010 Melbourne, Australia	Prospective cohort study	620 mother-child pairs	Duration of exclusive breastfeeding and partial breastfeeding (weeks)	Overweight/obesity (healthy vs. above healthy BMI) [measured at 10 years]	No association between breastfeeding and overweight/obesity in children at 10 years.
Queiroz et al., 2012 Laje & Mutuípe, Brazil	Prospective cohort study	373 mother-child pairs	Duration of exclusive breastfeeding (days)	LAZ (measured at 12 months)	Longer duration of exclusive breastfeeding was associated with higher LAZ in children.
Woo et al., 2013 United States, Mexico, and China	Prospective cohort study	365 mother-child pairs	Duration of exclusive breastfeeding (months)	WAZ, LAZ, BAZ (measured at 1 year)	Longer breastfeeding duration was associated with lower WAZ.
Nguyen et al., 2013 Hanoi, Vietnam	Prospective cohort study	964 mother-child pairs	Duration of exclusive breastfeeding (months)	Attained weight and length (measured at 2 years)	No association between exclusive breastfeeding and growth in children.
Caleyachetty et al., 2013 Mysore, India	Prospective cohort study	568 mother-child pairs	Duration of exclusive breastfeeding [1-4, 5-8, 9-12, 13-16, 17-20, ≥21 months]	High BMI (BMI>90th percentile) (measured at 5 years)	No association between breastfeeding and high BMI risk in children at 5 years.
Kattula et al., 2014 Southern India	Prospective cohort study	414 mother-child pairs	Duration of exclusive breastfeeding (<6 vs. 6 months)	Monthly gain of weight and length (measured from birth to 2 years)	Exclusive breastfeeding duration until 6 months was associated with lower monthly gain of weight and length in children at 2 years.
Oddy et al., 2014 Perth, Australia	Prospective cohort study	2868 mother-child pairs	Duration of breastfeeding (months)	Change in WAZ form birth and 1 year	Longer breastfeeding duration was associated with reduction in WAZ from birth to 1 year old in children.

Note: LAZ: Length-for-age z-score; HAZ: Height-for-age z-score; WAZ: Weight-for-age z-score; WLZ: Weight-for-length z-score; WHZ: Weight-for-height z-score

Table 2.11. Relationships between infant feeding practices and nutritional status in children (continued)

Reference and Study Location	Study design	Subjects	Exposure	Outcomes	Main findings
Budree et al., 2017 Paarl, South Africa	Prospective cohort study	386 mother-child pairs	Duration of exclusive breastfeeding (months)	WAZ, LAZ, BAZ (measured at birth and 1 year)	Longer duration of exclusive breastfeeding was associated with lower LAZ in children at 12 months.
Moschonis et al., 2017 UK, France, Greece, Portugal	Prospective cohort study	UK = 6522 France = 1070 Greece = 309 Portugal = 3387	Duration of breastfeeding [0, <1, 1-3, 3-6, ≥6 (Ref) months]	HAZ, overweight/obesity (measured at 4/5/9/13 years)	UK: Children who were never breastfed and breastfed between 1-3 months had a higher HAZ at 4 years of age compared to those who were breastfed ≥6 months. Children who were breastfed between 3-6 months were less likely to be overweight/obese at 4 and 13 years old compared to those who were breastfed ≥6 months France: Children who were never breastfed and breastfed between 1-6 months had a lower HAZ at 5 years old compared to those who were breastfed ≥6 months. Greece & Portugal: No association was found.
Olaya et al., 2017 Bogota, Colombia	Prospective cohort study	108 mother-child pairs	Duration of exclusive breastfeeding [4-5 vs. ≥6 months]	WLZ, LAZ, WAZ at 6 months, change from 0-6 months	No association exclusive breastfeeding and nutritional status in children.
Horta &Victoria, 2013	Systematic review and meta-analysis of 24 cross-sectional, 6 case-control, and 42 cohort studies		Duration of exclusive breastfeeding (different definition across studies)	Overweight, obesity	A reduction of about 10.0% in the prevalence of overweight or obesity was found in children with longer breastfeeding duration.
Age at introduction of complementary feeding					
Udoh & Amodu, 2016 Akpabuyo, Nigeria	Cross-sectional	330 children aged 6-11 months	Introduction of complementary foods between 6-8 months [yes (Ref) vs. no]	Stunting (LAZ<-2) Underweight (WAZ<-2) Wasting (WLZ<-2)	Children who did not receive timely complementary foods had higher risk for wasting.
Irarrázaval et al., 2018 Haiti	Cross-sectional	278 children aged <24 months	Introduction of complementary foods between 6-8 months (yes vs. no)	Stunting (LAZ<-2) Underweight (WAZ<-2) Wasting (WLZ<-2)	No association between introduction of complementary foods and undernutrition in children.
Abeway et al., 2018 Merhabete, Ethiopia	Cross-sectional	410 children aged 6-59 months	Introduction of complementary foods [at 6 months (Ref) vs. before and after 6 months]	Stunting (LAZ<-2)	Introduction of complementary feeding before and after 6 months were associated with increased risk of stunting in children.

Note: LAZ: Length-for-age z-score; HAZ: Height-for-age z-score; WAZ: Weight-for-age z-score; WLZ: Weight-for-length z-score; WHZ: Weight-for-height z-score

Table 2.11. Relationships between infant feeding practices and nutritional status in children (continued)

Reference and Study Location	Study design	Subjects	Exposure	Outcomes	Main findings
Nsereko et al., 2018 Rwanda, Africa	Cross-sectional	1634 children ≤2 years	Introduction of complementary foods between 6-8 months [yes vs. no (Ref)]	Stunting (LAZ<-2)	No association between introduction of complementary foods and stunting in children.
Ahmad et al., 2018 Aceh, Indonesia	Cross-sectional	392 children aged 6-23 months	Introduction of complementary foods between 6-8 months [<6 vs. ≥6 (Ref) months]	Stunting (LAZ<-2) Underweight (WAZ<-2) Wasting (WLZ<-2)	No association between introduction of complementary foods and undernutrition in children.
Huynh et al., 2019 Ho Chi Minh, Vietnam	Cross-sectional	225 children aged 6-59 months	Introduction of complementary foods between 6-8 months [<6 (Ref) vs. ≥6 months)	Stunting (LAZ<-2) Underweight (WAZ<-2) Wasting (WLZ<-2) Overweight (BAZ>+1)	Introduction of complementary feeding ≥6 months was associated with decreased risk of stunting in children.
Seach et al., 2010	Prospective cohort study	620 mother-child pairs	Age at introduction of solid foods (weeks)	Overweight/obesity (healthy vs. above healthy BMI) [measured at 10 years]	Delayed introduction of solid foods was associated with reduced risk overweight/obese in children at age 10 years.
Woo et al., 2013 United States, Mexico, and China	Prospective cohort study	365 mother-child pairs	Age at introduction of solid and semi-solid foods (months)	WAZ, LAZ, BAZ (measured at 1 year)	No association was found between the timing of complementary food introduction and nutritional status in children.
Caleyachetty et al., 2013 Mysore, India	Prospective cohort study	568 mother-child pairs	Age at introduction of solid and semi-solid foods [≤3, 4, 5, ≥6 months]	High BMI (BMI>90th percentile) (measured at 5 years)	No association between timing of complementary food introduction and high BMI risk in children at 5 years
Vail et al., 2015 Cambridge, UK	Prospective cohort study	571 mother-child pairs	Age at introduction of solid foods (months)	Weight z-score, length z-score, BAZ (measured at birth, 3 and 12 months)	Age introduction of solid foods was inversely associated with weight and BMI in children at 3 months. Age introduction of solid foods was inversely associated with weight and length in children at 12 months.
Moschonis et al., 2017 UK, France, Greece, Portugal	Prospective cohort study	UK = 6522 France = 1070 Greece = 309 Portugal = 3387	Age at introduction of complementary foods [<4, 4-5, 5-6, ≥6 months]	HAZ, overweight/obesity (measured at 4 /5 years)	Portugal: Children who were introduced with complementary foods ≥6 months had lower HAZ compared to those who were introduced between 5-6 months. UK, France, & Greece: No association was found.
Liu et al., 2019 Shaanxi, China	Prospective cohort study	1802 children aged 6-12 months	Introduction of complementary foods [<6, 6, >6 months)	HAZ, WAZ, WHZ (measured 4 times, once every 6 months)	No association was found between the timing of complementary food introduction and nutritional status in children.

Note: LAZ: Length-for-age z-score; HAZ: Height-for-age z-score; WAZ: Weight-for-age z-score; WLZ: Weight-for-length z-score; WHZ: Weight-for-height z-score

Table 2.11. Relationships between infant feeding practices and nutritional status in children (continued)

Reference and Study Location	Study design	Subjects	Exposure	Outcomes	Main findings
Mannan, 2018 southwestern Sydney, Australia	Prospective cohort study	346 mother-child pairs	Introduction of formula or solids [≤4 vs. >4 (Ref) months]	Overweight or obesity (BMI≥85th percentile) [measured from 0-1 year to 10-11 years]	Introduction of formula or solids ≤4 months was associated with increased risk of overweight or obesity in children.
Diet diversity					
Arimond & Ruel, 2004	Cross-sectional studies from 11 countries	Children age 6-23 months	Diet diversity [0-2 (Ref), 3-4, 5-7 food groups]	LAZ	Diet diversity was positively associated with LAZ in children from 7 countries, while the remaining 4 countries found no significant associations.
Udoh & Amodu, 2016 Akpabuyo, Nigeria	Cross-sectional	330 children age 6-11 months	Minimum dietary diversity [<4 vs. ≥4 (Ref) food groups]	Stunting (LAZ<-2) Underweight (WAZ<-2) Wasting (WLZ<-2)	Children who did not receive the minimum dietary diversity had higher risk for underweight and stunting.
Irarrázaval et al., 2018 Haiti	Cross-sectional	278 children <24 months	Minimum dietary diversity [<4 vs. ≥4 food groups]	Stunting (LAZ<-2) Underweight (WAZ<-2), Wasting (WLZ<-2)	No association between minimum dietary diversity and nutritional status in children.
Ahmad et al., 2018 Aceh, Indonesia	Cross-sectional	392 children aged 6-23 months	Minimum dietary diversity [<4 (Ref) vs. ≥4 food groups]	Stunting (LAZ<-2) Underweight (WAZ<-2), Wasting (WLZ<-2)	No association between minimum dietary diversity and nutritional status in children.
Mya et al., 2019 Myanmar	Cross-sectional	1222 children aged 6-23 months	Minimum dietary diversity [<4 vs. ≥4 food groups]	Stunting (LAZ<-2)	No association between minimum dietary diversity and stunting in children.
Walters et al., 2019 Walters, Africa	Cross-sectional	2294 children aged 0-23 months	Minimum dietary diversity [<4 (Ref) vs. ≥4 food groups]	Stunting (LAZ<-2) Underweight (WAZ<-2) Wasting (WLZ<-2)	No association between minimum diet diversity and nutritional status in children.
Budree et al., 2017 Paarl, South Africa	Prospective cohort study	398 mother-child pairs	Diet diversity scores at 9 and 12 months	WAZ, HAZ, BAZ (measured at birth and 1 year)	No association between diet diversity score and nutritional status in children at 12 months.
Fernandez et al., 2016 Southeast Michigan, US	Prospective cohort study	264 mother-child pairs	Diet diversity scores at mean 4.2 years of age	BAZ change per year (measured at mean 6 years old)	Dietary diversity was positively associated with annual increases in BAZ,
Prado et al., 2019 Ghana, Malawi, & Burkina Faso, Africa	4 prospective cohort studies	Ghana = 1039, Malawi = 684, 1504, Burkina Faso = 2619	Diet diversity between 9-18 months	LAZ (measured at 18 months)	Higher diet diversity was associated with higher LAZ in children from Malawi and Burkina Faso at 18 months.

Note: LAZ: Length-for-age z-score; HAZ: Height-for-age z-score; WAZ: Weight-for-age z-score; WLZ: Weight-for-length z-score; WHZ: Weight-for-height z-score

WAZ (Moschonis et al., 2017; Oddy et al., 2014; Woo et al., 2013), lower weight and height gain (Kattula et al., 2014), and higher LAZ (Queiroz et al., 2012) in children during the first two years of life. Inconsistent findings have also been reported in previous studies whereby shorted breastfeeding duration less than six months was associated with reduced risk of overweight (Campbell et al., 2018; Moschonis et al., 2017), higher risk of underweight and stunting (Irarrázaval et al., 2018), and higher HAZ (Moschonis et al., 2017) in children. Meanwhile, findings from four prospective cohort studies found no significant associations between breastfeeding and nutritional status in children (Caleyachetty et al., 2013; Nguyen et al., 2013; Olaya et al., 2017; Seach et al., 2010).

Inappropriate feeding practice such as too early or too late introduction of complementary foods may also lead to persistent child malnutrition. Early introduction of complementary foods may predispose the infants to reduced protective benefits of breast milk and increased the risk of insufficient energy and nutrient intake by the infants (Michaelsen et al., 2003). In contrast, a delayed introduction of complementary foods might not be able to supply the full range and quantities of nutrients required to support the rapid growth of infants at 6 months of age onwards and lead to increased risk of growth faltering and malnutrition among infants (Muhimbula & Issa-Zacharia, 2010). Findings from previous studies (Table 2.11) showed that timely introduction of complementary feeding was associated with a lower risk of wasting, stunting, overweight, and obesity, and lower HAZ in children (Abeway et al., 2018, Huynh et al., 2019; Mannan, 2018; Seach et al., 2010; Moschonis et al., 2017; Udoh & Amodu, 2016; Vail et al., 2015), while other studies have found no association between age at introduction of complementary feeding and nutritional status (Ahmad et al., 2018; Caleyachetty et al., 2013; Irarrázaval et al., 2018; Liu et al., 2019; Nsereko et al., 2018; Woo et al., 2013).

The WHO has recommended that infant and young children should receive the minimum diet diversity for at least four food groups during the complementary feeding period (WHO 2008). While some studies reported that children who received a more diverse diet had a lower risk of underweight and stunting (Udoh & Amodu, 2016), as well as higher LAZ and BAZ (Arimond & Ruel, 2004; Fernandez et al., 2016; Prado et al., 2019), others have found no significant associations (Ahmad et al., 2018; Budree et al., 2017; Irarrázaval et al., 2018; Mya et al., 2019; Walters et al., 2019).

Several reasons may explain the inconsistent findings across studies. Firstly, the adjustment for multiple confounders tended to attenuate the protective effect of prolonged breastfeeding duration. Secondly, the instruments used to assess infant feeding practices, classification of the infant feeding indicators, and outcomes measured were varied across studies. Thirdly, the duration of follow-up and age at which outcomes were assessed may contribute to the inconsistent findings across studies. Although inconsistent findings have been reported, findings from previous studies have demonstrated the critical role of infant feeding practices on the child's nutritional status. More studies are needed to identify the optimal feeding practices especially during the window of opportunity to ensure proper growth and prevent all forms of malnutrition in children.

2.6 Interrelationships between Maternal Vitamin D Status, Infant Feeding Practices, Childhood Allergic Diseases, and Malnutrition

Allergic diseases and malnutrition are major public health problems in children during the first 2 years of life, given their high prevalence and adverse health consequences (Ang et al., 2014; Hill & Spergel, 2018; Ijarotimi, 2013; Pawankar, 2014; Zheng et al., 2011). Research suggests that both allergic diseases and malnutrition can occur simultaneously in children and are interrelated (Beck et al., 2016; Berents et al., 2017; Chong et al., 2018; El-Heis et al., 2018; Flammarion et al., 2011). In a two-year prospective cohort study (Table 2.12), Berents et al. (2017) found that infants with a higher weight-for-length at 0-12 months were at a higher risk of eczema at 2 years of age. Another study by El-Heis et al. (2018) revealed that infants with linear growth faltering during the in-utero period and the first 6 months of life were more likely to develop eczema at 12 months of age. Studies by Berents et al. (2017) and El-Heis et al. (2018) indicates that malnutrition at birth and early infancy is linked with the development of childhood allergy. A large prospective cohort study among 5276 infants in Australia found that infants with both food allergy and eczema were shorter and lighter during the first year of life and continued to grow slowly at 4 years of age (Beck et al., 2016). Similar findings were also reported in several small cross-sectional studies that children with food allergy and eczema were more likely to be stunted and underweight (Chong et al., 2018; Flammarion et al., 2011; Meyer et al., 2004). Findings from these studies demonstrated an association between allergic diseases and malnutrition, highlighting the need to identify the shared risk and protective factors for allergic diseases and malnutrition which may be targeted in prevention strategies.

A review of the literature suggests that research assessing the shared risk and protective factors for allergic diseases and malnutrition is lacking, although there are studies that assessed these outcomes separately. As discussed earlier, maternal vitamin D levels in the prenatal period and infant feeding in the postnatal period can influence the risk of allergic diseases and malnutrition, respectively (Blomberg et al., 2017; Mannan, 2018; Morales et al., 2015; Taylor-Robinson et al., 2016). Previous studies found that low maternal vitamin D levels can be a risk factor for childhood allergy (Blomberg et al., 2017; Chiu et al., 2015) and malnutrition (Morales et al., 2015; Toko et al., 2016), respectively. In addition, longer breastfeeding duration, early introduction of complementary foods, and introduction of a less diverse food groups can increase allergy risk in children (Gao et al., 2019; Roduit et al., 2014; Taylor-Robinson et al., 2016). Meanwhile, breastfeeding, timely introduction of complementary feeding, and introduction of at least 4 food gourds are protective against childhood malnutrition (Horta & Victoria, 2013; Huynh et al., 2019; Mannan, 2018; Udoh & Amodu, 2016; Yan et al., 2014).

To our best knowledge, no studies have been conducted to determine the interrelationships between maternal vitamin D status, infant feeding practices, development of allergic diseases, and malnutrition in children. Hence, studies are needed to assess the influences of maternal vitamin D status and infant feeding practices on childhood allergy and malnutrition simultaneously and the interrelationships between theses factor and outcomes.

Table 2.12. Relationships between malnutrition and allergic diseases

Study (Country)	Subjects	Exposure	Outcomes	Study design	Main findings
Berents at al., 2017 (Norway)	404 infants with acute bronchiolitis and 238 from general population (aged 0-12 years old)	WLZ	Eczema (Hanifin & Rajka criteria / DD)	Prospective cohort	Infants with a higher WLZ at enrolment were at a higher risk of eczema at enrolment (OR = 3.03, 95% CI = 1.23-7.50) and two years old (OR = 2.40, 95% CI = 1.11-5.17).
El-Heis at al., 2018 (UK)	1759 infants at birth and followed up at 6 and 12 months	Linear growth velocities	Eczema (UK Working Party diagnostic criteria)	Prospective cohort	Lower linear growth velocities at birth (OR = 0.80, 95% CI = 0.65-0.98) and 6 months (OR = 0.80, 95% CI = 0.66-1.00) were associated with eczema at 12 months.
Beck et al., 2016 (Australia)	5276 children recruited at aged 1 year and followed up at 4 years old	Food allergy (OFC) Eczema (PP)	Weight, height	Prospective cohort	Children with both food allergy and eczema were shorter and lighter during the first year of life and continued to grow slow at 4 years of age.
Chong et al., 2018 (Singapore)	74 children aged 0-12 years old with any food allergy	Food allergy (SPT/sIgE/FE/ OFC) Other atopic diseases (PP)	WHZ, WAZ, HAZ	Cross-sectional	Children with eczema and food allergies were more likely to be stunted.
Meyer et al., 2004 (UK)	97 children aged 0-16 years old with food allergy	Food allergy (SPT/sIgE/FE)	WHZ, WAZ, HAZ	Cross-sectional	Children with food allergies and had food elimination of ≥3 foods were more likely to be underweight.
Flammarion et al., 2011 (France)	96 children (6 months - <15 years) with food allergy and 95 children without food allergy	Food allergy (SPT/sIgE/FE/ OFC)	WHZ, WAZ, HAZ	Cross-sectional	Children with food allergies had lower WAZ and HAZ compared to children without food allergy.

Note: PR: parent-reported; DD: Doctor-diagnosed; SPT: skin prick test; sIgE: serum allergen-specific IgE blood test; FE: Food elimination; OFC: oral food challenge; WAZ: weight-for-age z scores; HAZ: height-for-age z-scores; WHZ: weight-for-height z scores; WLZ: weight-for-length z scores

Chapter 3

Methodology

3.1 Study Design

The present study is a prospective cohort study that is initiated to determine the associations of maternal vitamin D status during late pregnancy and infant feeding practices with the development of allergic diseases and malnutrition in infants. Pregnant women were recruited during the third trimester and their child was followed up prospectively at 3-, 6-, and 12-month of age. This study is part of the Mother and Infant Cohort Study (MICOS) and the protocol of MICOS has been previously described by Woon et al. (2018) (Appendix 1).

3.2 Study Setting

This study was conducted at government Maternal and Child Health (MCH) clinics located in the states of Selangor and Kuala Lumpur in Malaysia. Selangor is the most populous state in Malaysia and encompasses a land area of 8104 km^2. Meanwhile, Kuala Lumpur is the most densely populated state in Malaysia and encompasses a land area of 243 km^2. Both Selangor and Kuala Lumpur are the most urbanized states in Malaysia with rapid urban growth (Department of Statistics Malaysia, 2010). Urbanisation has been linked with increased risk of allergic diseases (Nicolaou, Siddique, & Custovic, 2005; Schröder, Li, Wong, & Schaub, 2015) and allergic diseases have been linked with malnutrition in infants and children (Berents et al., 2017; Chong et al., 2018; Meyer et al., 2014). Considering the links between study area, allergic diseases, and malnutrition, conducting the study in the urban area of the two states in Malaysia could minimise the confounding bias caused by study area. The MCH clinics are the primary source providing regular antenatal and postnatal care to women and children in Malaysia. The MCH clinics are easily accessible as up to 90.0% of the population lived within a 5-km radius from the health care facility (Rugayah et al., 2000). In addition, health care costs in government facilities are highly subsidised; therefore, the charges are very low and affordable by individuals from different SES (Rugayah et al., 2000). Thus, recruiting respondents from the MCH may be representative of the overall population as it consists of respondents from diverse ethnicity and different SES level.

3.3 Study Respondents

Pregnant women were recruited during the third trimester of pregnancy and followed up prospectively until their child was 12 months of age. The inclusion criteria were that respondents were Malaysian women, aged 18-40 years, gestational age ≥ 28 weeks based on the last menstrual period or early ultrasound examination, singleton pregnancy, and attending the

selected health clinics for a regular medical check-up. Women with multiple pregnancies, a preterm birth at less than 37 weeks gestation, diagnosed with an immune deficiency, or a child born with congenital abnormalities were excluded.

3.4 Sample Size Calculation

Table 3.1 shows the sample size calculation for each of the objectives. Objective 1 was calculated using the formula for prevalence study (Daniel, 1999). Objective 2 was calculated using the formula for cohort study (Schlesselman, 1974) with 95% power and 5% significance level. Objective 3 was calculated by using the rule of thumb for Structural Equation Modelling (SEM) (Hair, Black, Babin, & Anderson, 2014; Kline, 2011; Nunnally, 1967). Based on the sample size calculated for all study objectives, the highest sample size N = 356 was selected to ensure sufficient precision for the estimate of the outcomes.

Table 3.1. Sample size calculation

<table>
<tr><td colspan="2">Objective 1a: To determine the prevalence of allergic diseases in infants during the first year of life.</td></tr>
<tr><td>$N = \frac{Z^2 P(1-P)}{d^2}$
(Daniel, 1999)
$N = \frac{1.96^2(0.167)(1-0.167)}{0.05^2}$
= 214 respondents</td><td>where
N = sample size
Z = Z statistic for a level of confidence = 1.96
P = expected prevalence of eczema
= 16.7% = 0.167 (Goh et al., 2018)
d = precision = 0.05</td></tr>
<tr><td colspan="2">Objective 1b: To determine the prevalence of malnutrition in infants during the first year of life.</td></tr>
<tr><td>Stunting, P = 0.221 (IPH, 2016a)
Z = 1.96, d = 0.05
$N = \frac{1.96^2(0.221)(1-0.221)}{0.05^2}$
= 265 respondents</td><td>Underweight, P = 0.147 (IPH, 2016a)
Z = 1.96, d = 0.05,
$N = \frac{1.96^2(0.147)(1-0.147)}{0.05^2}$
= 193 respondents</td></tr>
<tr><td>Wasting, P = 0.112 (IPH, 2016a)
Z = 1.96, d = 0.05
$N = \frac{1.96^2(0.112)(1-0.112)}{0.05^2}$
= 153 respondents</td><td>Overweight, P = 0.041 (IPH, 2016a)
Z = 1.96, d = 0.05,
$N = \frac{1.96^2(0.041)(1-0.041)}{0.05^2}$
= 60 respondents</td></tr>
<tr><td colspan="2">Objective 2a: To determine the association between maternal vitamin D status and development of allergic diseases in infants.</td></tr>
<tr><td colspan="2">$N = \frac{\left[Z_\alpha\sqrt{2\overline{pq}} + Z_\beta\sqrt{p_1(1-p_1)-p_2(1-p_2)}\right]^2}{(p_1-p_2)^2}$
(Schlesselman, 1974)
where</td></tr>
</table>

N = sample size

p_1 = probability of allergy in infants with sufficient maternal vitamin D

= 0.1875 (Chiu et al., 2015)

p_2 = probability of allergy in infants with insufficient maternal vitamin D

= 0.1136 (Chiu et al., 2015)

$\bar{p} = (p_1 + p_2)/2$ = (0.1875 + 0.1136) / 2 = 0.1506

$\bar{q}$ = 1 – $\bar{p}$ = 1 – 0.1506 = 0.8494

Z_α= standard normal variate for level of significance (5% significance level) = 1.96

Z_β= standard normal variate for power or Type II error (95% power) = 1.645

$$N = \frac{\left[1.96\sqrt{2(0.1506)(0.8494)} + 1.645\sqrt{0.1875(1-0.1875) - 0.1136(1-0.1136)}\right]^2}{(0.1875 - 0.1136)^2}$$

= 341 respondents

Objective 2b: To determine the association between maternal vitamin D status and development of malnutrition in infants.

p_1 = probability of malnutrition in infants with sufficient maternal vitamin D

= 0.093 (Toko et al., 2016)

p_2 = probability of malnutrition in infants with insufficient maternal vitamin D

= 0.400 (Toko et al., 2016)

$\bar{p} = (p_1 + p_2)/2$ = (0.093 + 0.400) / 2 = 0.2465

$\bar{q}$ = 1 – $\bar{p}$ = 1 – 0.2465 = 0.7535

Z_α= standard normal variate for level of significance (5% significance level) = 1.96

Z_β= standard normal variate for power or Type II error (95% power) = 1.645

$$N = \frac{\left[1.96\sqrt{2(0.2465)(0.7535)} + 1.645\sqrt{0.093(1-0.093) - 0.400(1-0.400)}\right]^2}{(0.093 - 0.400)^2}$$

= 36 respondents

Objective 2c: To determine the association between infant feeding practices and development of allergic diseases in infants.

p_1 = probability of allergy in infants who were introduced with complementary feeding at ≥ 6 months = 0.1585 (Gao et al., 2019)

p_2 = probability of allergy in infants who were introduced with complementary feeding at < 6 months = 0.2375 (Gao et al., 2019)

$\bar{p} = (p_1 + p_2)/2$ = (0.1585 + 0.2375) / 2 = 0.1980

$\bar{q}$ = 1 – $\bar{p}$ = 1 – 0.1980 = 0.8020

Z_α= standard normal variate for level of significance (5% significance level) = 1.96

Z_β= standard normal variate for power or Type II error (95% power) = 1.645

$$N = \frac{\left[1.96\sqrt{2(0.1980)(0.8020)} + 1.645\sqrt{0.1585(1-0.1585) - 0.2375(1-0.2375)}\right]^2}{(0.2481 - 0.1715)^2}$$

= 343 respondents

Objective 2d: To determine the association between infant feeding practices and development of

malnutrition in infants.
p_1 = probability of malnutrition in infants who were breastfed for > 4 months = 0.4462 (Carling, Demment, Kjolhede, & Olson, 2015) p_2 = probability of malnutrition in infants who were breastfed for ≤ 4 months = 0.5238 (Carling et al., 2015) $\bar{p} = (p_1 + p_2)/2$ = (0.4462 + 0.5238) / 2 = 0.4850 $\bar{q}$ = 1 – $\bar{p}$ = 1 – 0.4850 = 0.5150 Z_α= standard normal variate for level of significance (5% significance level) = 1.96 Z_β= standard normal variate for power or Type II error (95% power) = 1.645 $N = \frac{\left[1.96\sqrt{2(0.4850)(0.5150)} + 1.645\sqrt{0.4462(1-0.4462) - 0.5238(1-0.5238)}\right]^2}{(0.4462-0.5238)^2}$ = 356 respondents
Objective 3: To determine the interrelationships between maternal vitamin D status, feeding practices, development of allergic diseases, and malnutrition in infants.
Rule of thumb for structural equation model (SEM): a) A model containing five or fewer constructs requires a minimum sample size of 100-150 respondents (Hair et al., 2014) b) 20 observations per estimated parameter: 17 parameters*20 = 340 respondents (Kline, 2011) c) 10 cases per variable: 5 variables*10 = 50 respondents (Nunnally, 1967)

In order to correct the loss of sampling efficiency during the sampling procedures, the design effect should be taken into account when determining the sample size (Magnani, 1997). The design effect (D) was determined using the following formula (Antonisamy, Christopher, & Samuel, 2010):

$$D = 1 + (m - 1)\,ICC$$

where,

D = design effect

m = estimated cluster size = 100

ICC = intraclass correlation coefficient = 0.001 (Kramer et al., 2007)

Thus,

D = 1 + (100 – 1) 0.001

= 1.099

Taking account for design effect (1.099), the sample size is increased by

n = 356 x 1.099

= 391 respondents

Taking account for attrition rate (28.5%) (Zalbahar et al., 2016), the sample size is increased by

N = 391 + (391 x 0.285)

= 502 respondents

A minimum total of 356 respondents were required for this study. By taking into consideration the design effect and attrition rate, the desired sample size for this study was increased to 502 respondents.

3.5 Sampling

Figure 3.1 presents the sampling procedures of the study. A list of government health clinics in Kuala Lumpur and Selangor was obtained from the Selangor and Kuala Lumpur Health Department. Government-funded health clinics which consist of an MCH section were included in the sampling frame. Probability proportional to size cluster sampling method was used during the selection of health clinics. According to the records at health clinics, the total number of pregnant women who visited the health clinics in Kuala Lumpur and Selangor in a day were 60 and 100, respectively. With an average health clinic size of 60 in Kuala Lumpur and 100 in Selangor, 6 health clinics [$\frac{502}{(60+100)/2}$ = 6] were required to achieve the target sample size. According to the 2016 Malaysia Health Indicators (MOH, 2016b), there was a total of 255,932 and 1,105,693 antenatal attendances in Kuala Lumpur and Selangor, respectively. By taking into account of the ratio of antenatal attendances in Kuala Lumpur and Selangor (1:4.3), 1 health clinic in Kuala Lumpur and 5 health clinics in Selangor were randomly selected by using a random number generator (Randomness and Integrity Services Ltd, 1998). All pregnant women who attended the selected health clinics for antenatal check-up and met the inclusion criteria were invited to participate in the study.

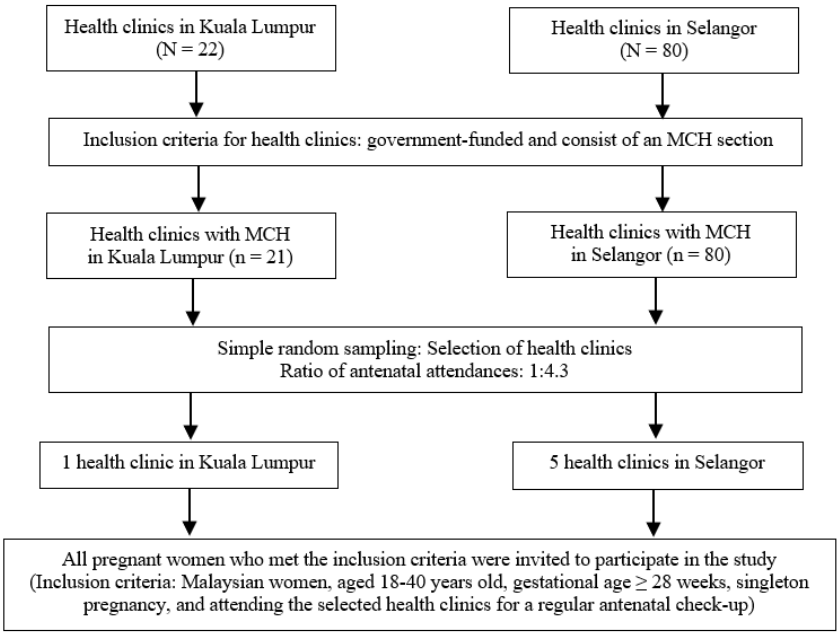


Figure 3.1. Sampling Procedures

3.6 Ethical Clearance

Approvals of the study protocol were obtained from the Ethics Committee for Research Involving Human Subjects, Universiti Putra Malaysia (JKEUPM) (Appendix 2) and Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (Appendix 3). Permission to conduct the study at the selected government health clinics were obtained from the State Health Department (Appendix 4 and 5) and District Health Office (Appendix 6 and 7).

3.7 Translation of Questionnaire

The original English questionnaire was translated to Malay and Chinese, respectively by two study researchers; one was from a Malay educational background and one was from a Chinese educational background. Both study researchers have a background in health sciences and were proficient in both English and their native language. The translated questionnaire was back-translated to English by another two study researchers who were also fluent in English and their native language. The original English questionnaire and the back-translated versions were reviewed by two independent English reviewers and both reviewers agreed that the translated and back-translated questionnaires were consistent with each other.

3.8 Pre-testing of Questionnaire

The translated questionnaire was pre-tested among pregnant women who attended a MCH clinic that was not included in the present study to determine the face validity and to ensure clarity and ease of understanding of the questionnaire. During the pre-test, pregnant women were interviewed by the researchers using the translated questionnaire. The pregnant women were asked to inform the researchers on the words or sentences that were difficult to understand. Overall, the pregnant women clearly understood the questions and completed the interviews within 15 minutes. When the question “Have you or your family members had any of the following allergic diseases (food allergy/eczema/rhinitis/asthma)?” was asked, the pregnant women were unsure about the symptoms of some allergic diseases such as rhinitis. Thus, a short explanation on the symptoms for each allergic disease; namely, food allergy (had rash in the skin and sickness within two hours of eating some food and the symptoms repeated each time the same food was eaten), eczema (had itchy skin condition that affect the skin creases such as fronts of elbows, behind the knees, fronts of ankles, around the neck, or eyes), asthma (had symptoms such as coughing, wheezing, chest tightness, and shortness of breath), and rhinitis (had symptoms such as runny nose, sneezing, itching, and watery eyes after exposure to specific substances such as dust, animal hair, and pollen) was added.

3.9 Data Collection

The study visits were scheduled at the selected health clinics on four occasions; at the third trimester of pregnancy and 3, 6, and 12 months after delivery, respectively. The details of the variables assessed at each assessment point are shown in Figure 3.2. Pregnant women recruited during their third trimester were interviewed once at the selected health clinics for information on monthly household income, family history of allergic diseases, use of antibiotic during pregnancy, vitamin D intake and supplementation, and sun exposure. Meanwhile, a blood sample was collected from the pregnant women to determine their vitamin D status at third trimester. Information on maternal characteristics, obstetrical history, and anthropometric data were obtained from their medical records during the third trimester visit.

After childbirth, postnatal visits were conducted when the infants were 3-, 6-, and 12-month of age. The follow-up time points were selected in accordance with the immunisation schedule in the health clinic, where mothers were expected to bring their infants to the health clinics for vaccination. The first follow-up time point at 3 months was selected because eczema commonly occurs between 3 to 6 months of age in infants (Bernard & Eichenfield, 2007). Information on infant characteristics were obtained from their medical records during the first postnatal visit at 3 months. Mothers were asked questions on infant feeding practices, symptoms on eczema and food allergy in their child, and environmental factors at each postnatal visit. In addition, anthropometric data of infants were extracted from their medical records during the postnatal visit. Serum samples were collected from the infants at 12 months of age to determine their serum allergen-specific IgE levels.

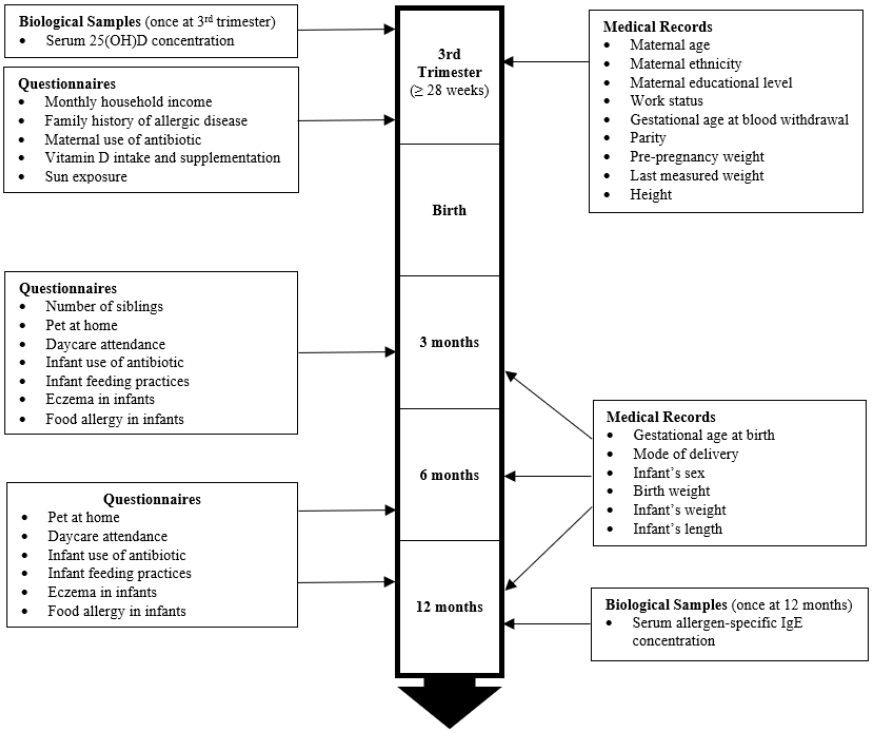


Figure 3.2. Data Collection and Study Timeline

3.10 Flow of Respondents in the Study

Figure 3.3 presents the flow chart of study respondents. Between November 2016 and January 2018, a total of 3982 pregnant women who met the inclusion criteria were invited to participate in the study. An information sheet that explains the purpose of the study was distributed to the pregnant women and written informed consent was obtained from those who agreed to participate in the study (Appendix 8).

Of the 3982 pregnant women being invited to the present study, 557 consented to participate, 2896 were not interested and refused to participate in the study, 500 refused because they will move out of the study area after giving birth, and 29 refused due to parental worries concerning blood taking of their child. Of the 557 pregnant women who consented, 535 completed the interview session at the third trimester of pregnancy and 22 pregnant women were excluded because they did not continue their antenatal check-up at the clinics and thus, unable to obtain their serum sample for 25(OH)D analysis.

Of the 535 infants delivered, 430 mother-infant pairs completed the 3 months follow-up. A total 105 mother-infant pairs were excluded from the study at 3 months follow-up due to preterm delivery (21 infants), infant death (1 infant), infant born with congenital abnormalities (1 infant), infant developed severe illness (1 infant), respondents move out of the study area (33 mother-infant pairs), and 48 mothers refused to continue the study. A total of 406 mother-infant pairs completed the 6 months follow-up. Of the 24 mother-infant pairs excluded at 6 months follow-up, 7 moved out of the study area and 17 not willing to continue. The final sample size was 380 mother-infant pairs with 26 mother-infant pairs excluded due to 11 moved out of study area, 14 were not willing to continue, and 1 infant passed away. At 12 months follow-up, serum IgE measurements were analysed in 314 infants and 66 infants did not have serum IgE measurements due to 62 mothers not willing to give child samples and 4 infants had insufficient serum samples for IgE analysis.

There were no significant differences in characteristics of the respondents in terms of maternal age, ethnicity, educational level, work status, parity, pre-pregnancy BMI, gestational weight gain, family history of allergic disease, and maternal vitamin D status during late pregnancy between the 380 mother-child pairs who completed the 12 months follow-up and those loss to follow-up except for monthly household income (results shown in Appendix 9). Overall, it can be said that the final cohort of the present study is representative of the original cohort.

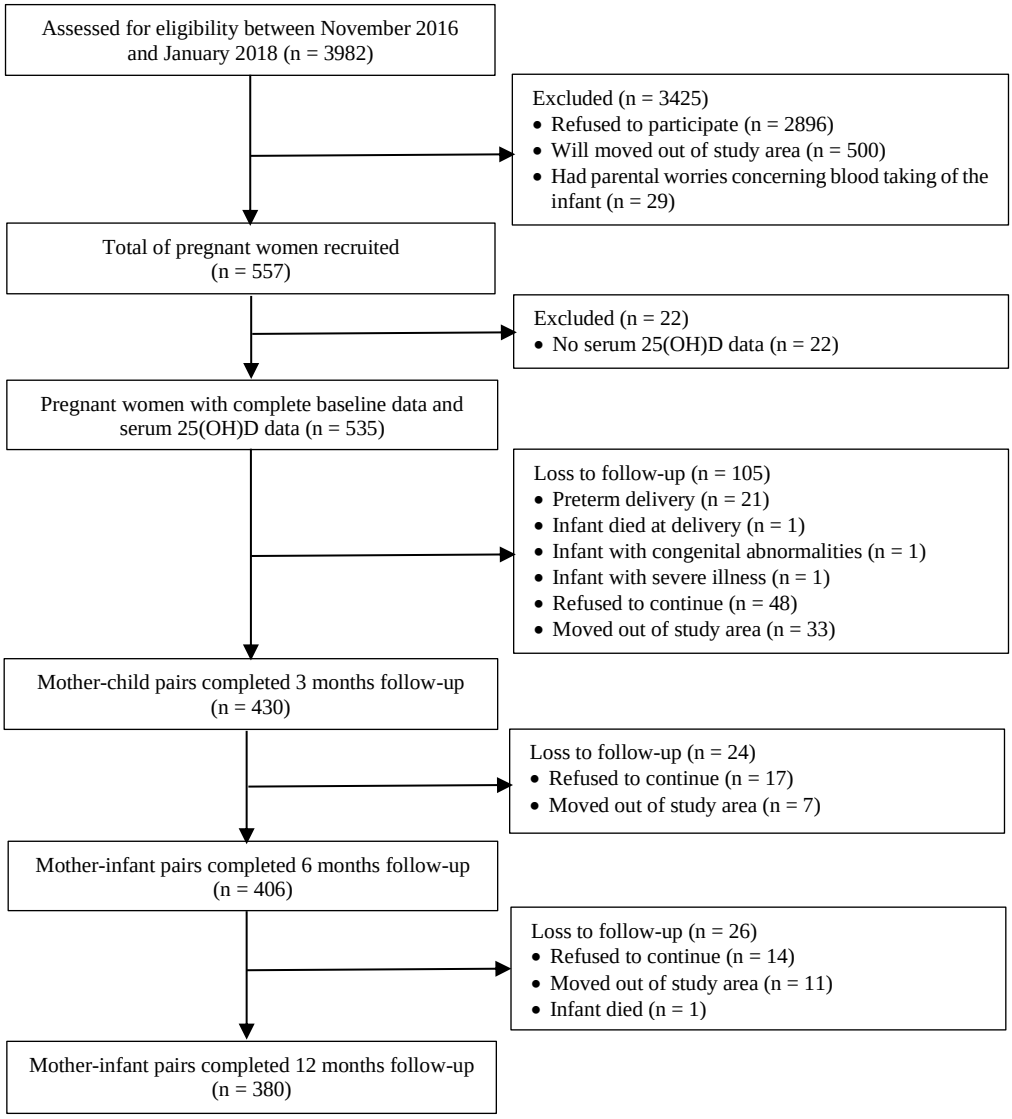


Figure 3.3. Flow Chart of Study Respondents

3.11 Medical Records

Information on maternal characteristics, obstetrical history, and infant characteristics were obtained from medical records at the health clinic.

i. **Maternal characteristics:** Information on maternal age at the time of delivery, ethnicity, educational level, work status, and gestational age at blood withdrawal were obtained at third trimester of pregnancy.

ii. **Obstetrical history:** Information on parity, pre-pregnancy weight, height, and last measured weight were obtained at third trimester of pregnancy. Pre-pregnancy BMI was calculated by dividing the pre-pregnancy weight in kilograms with the square of height in meters and classified into three categories; namely underweight (< 18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight/obesity ($\geqslant$ 25.0 kg/m^2) (WHO, 1995b). Gestational

weight gain was calculated as the difference between the final recorded body weight at the last prenatal visit and the pre-pregnancy weight recorded at the first prenatal visit and categorised as inadequate, adequate, or excessive GWG (Institute of Medicine, 2009).

iii. **Infant characteristics:** Information on gestational age at birth, mode of delivery, and infant's sex were obtained at 3-month follow up. Body weight and recumbent length of the infants at birth, 3, 6, and 12 months of age were extracted and converted to z-scores using the Anthro software version 3.2.2 (WHO, 2010a). Infants with LAZ < -2 were classified as stunted, WAZ < -2 were classified as underweight, WLZ < -2 were classified as wasted, and BAZ > +2 were classified as overweight based on 2006 WHO Child Growth Standards (WHO, 2006).

3.12 Biochemical Assessments

3.12.1 Maternal Vitamin D Status during Late Pregnancy

Maternal vitamin D status was measured once during the third trimester of pregnancy. Previous studies have shown that serum 25(OH)D concentration was highest during the third trimester of pregnancy and was significantly associated with serum 25(OH)D and health outcomes of the infants (Agudelo-Zapata et al., 2018; Bärebring et al., 2018; Thomas, Fudge, Whiting, & Coates, 2011). A venous blood sample (2mL) was collected from pregnant women during their routine antenatal check-up by trained nursing staff at the health clinics. Once collected, the blood sample was transferred to the blood collection tube and stored in the container provided by the laboratory at 2-8°C. Blood samples were then sent to the laboratory (Pantai Premier Pathology Sdn. Bhd.) within 24 hours for processing. At the laboratory, the blood samples were analysed by the trained laboratory staff using the Siemens ADVIA Centaur Vitamin D Total assay (Siemens, Tarrytown, NY, USA) to determine the serum 25(OH)D concentration. The assay has been standardised to the University of Ghent reference measurement procedure and has achieved the Centers for Disease Control Vitamin D Standardization Certification (Greg Miller et al., 2011; Sempos et al., 2012; Stepman, Vanderroost, Van Uytfanghe, & Thienpont, 2011; Thienpont, Stepman & Vesper, 2012). Maternal vitamin D status is classified as deficiency (< 30.0 nmol/L), insufficiency (30.0-49.9 nmol/L), and sufficiency (≥ 50.0 nmol/L) (Institute of Medicine, 2011).

3.12.2 Food Sensitisation

A peripheral venous blood sample of 1-2 mL was withdrawn via venepuncture in the dorsum of an infant's hand by a trained medical assistant at the health clinic at 12-month follow up. The blood sample was transferred into a serum separator tube and stored in the container provided by the laboratory at 2-8°C. Blood samples were sent to the laboratory (Acutest Systems (M) Sdn. Bhd, Kuala Lumpur) within 24 hours from the time of specimen collection for processing. The serum allergen-specific IgE levels against 19 food allergens, namely egg yolk, egg white,

soybean, peanut, milk, clam, crab, shrimp, codfish, tuna, salmon, wheat, chicken, beef, rice, banana, orange, sesame seed, and chocolate were analysed by the trained laboratory staff using the OPTIGEN Allergen-Specific IgE Assay (Hitachi Chemical Diagnostics, Inc., Mountain View, CA). The serum samples were first centrifuged for 10-20 minutes at 2500-3600 rpm and added to the test chambers which contain the food allergens. After a period of incubation and washes, an enzyme-labelled anti-IgE antibody was added to the test chambers. After a second washing, a luminescent reagent was added. The luminescent reagent combined with the enzyme-labelled anti-IgE antibody and generated a light. The amount of light emitted was measured in terms of net luminescence units (LU) by using the Chemiluminescent Assay (CLA) Luminometer. A level of specific IgE < 27 LU is rated as class 0, 27-65 LU as class 1, 66-142 LU as class 2, 143-242 LU as class 3, and >242 LU as class 4, respectively. Infants with a specific IgE level of class ≥ 1 were defined as having food sensitisation (Han et al., 2013; Wolthers & Staberg, 2013).

3.13 Questionnaires

Questions on potential confounding variables, infant feeding practices, and infant's development of allergic diseases were included in the questionnaires (Appendix 10 and 11). The questionnaires were administered by trained researchers through face-to-face interviews with the pregnant women.

3.13.1 Maternal Characteristics

Information on monthly household income was obtained at third trimester of pregnancy and categorised as low (< RM 2300), moderate (RM 2300 - RM 5599), and high (≥ RM 5600) (The Economic Planning Unit, 2010). 1 US dollar = RM 4.44 (as of March 24, 2020).

3.13.2 Maternal Vitamin D Intake and Supplementation

A semi-quantitative Vitamin D Food Frequency Questionnaire (FFQ) (Zaleha et al., 2015) was used to determine maternal vitamin D intake and supplementation in the third trimester of pregnancy. The vitamin D FFQ consists of 45 foods items derived from three categories: (i) foods that naturally contained vitamin D; (ii) foods that were fortified with vitamin D; and (iii) supplements that contained vitamin D. Pregnant women were required to recall their intake frequency and portion size for each of the food items consumed in the past one month. Portion size of the foods consumed was estimated using the household measures. As vitamin D content is not available in Malaysian food composition table, the vitamin D content of raw food was obtained from the United States Department of Agriculture National Nutrient Database for

Standard Reference (US Department of Agriculture, 2016) and Food Composition System Singapore. Meanwhile, vitamin D content of the fortified commercial products including milk and milk products, canned fish, bread spread, beverages, cereal and cereal products, and supplements were obtained from the products' label. The daily average vitamin D intake (μg/day) was calculated by multiplying the frequency of consumption per day, portion size consumed, and vitamin D content of the food. The vitamin D intake was then compared with the Recommended Nutrient Intakes (RNI) for Malaysians (NCCFN, 2017) to determine the nutrient intake adequacy.

3.13.3 Maternal Sun Exposure

Maternal sun exposure was assessed by using a Seven-day Sun Exposure Recall (Hall et al., 2010) during the third trimester of pregnancy. Pregnant women were required to record their outdoor activities over the past one week (from 7am to 7pm) in terms of type of activity, duration (in minutes), frequency (per week), clothing, sunscreen use, gloves, and umbrellas. Body surface area (BSA) exposed to sunlight was estimated by using the "Rule of Nine" and sun exposure index (SEI) was calculated by multiplying the amount of time spent outdoors with BSA exposed (Hall et al., 2010).

3.13.4 Family History of Allergic Diseases

Information on family history of allergic diseases was self-reported by the pregnant women at third trimester. It is defined as any of the infant's first-degree relatives (parents and sibling) having one or more history of eczema, food allergy, asthma or allergic rhinitis and the response options were "yes" or "no".

3.13.5 Environmental Factors

Maternal antibiotic use in pregnancy was self-reported by the pregnant women at third trimester. Information on number of siblings, pets at home during the first year, infant's daycare attendance during the first year, and infant's antibiotic use during the first year were self-reported by the mothers during postnatal follow up at 3, 6, and 12 months. Response options were "yes" or "no" for all variables.

3.13.6 Infant Feeding Practices

Three Infant and Young Child Feeding (IYCF) indicators, namely, exclusive breastfeeding, introduction of complementary foods, and minimum dietary diversity were adapted from the

Malaysian NHMS 2016 (IPH, 2016b) and WHO IYCF Indicators (WHO, 2010b). The IYCF indicators is a valid and reliable tool to assess infant and young child feeding practices at the population level as the indicators were validated using datasets from 10 different sites in developing countries (Working Group on Infant and Young Child Feeding Indicators, 2006; 2007). Infant feeding practices were self-reported by mothers at 3, 6, and 12 months follow up. The mothers were asked if their child was being breastfed and were any liquids or foods given to their child in the last 24 hours using a list of liquids and foods provided in the Malaysian NHMS 2016 (IPH, 2016b). The liquids and foods given were then assigned into 7 food groups; namely, (1) grains, roots and tubers (such as rice, porridge, and potato), (2) legumes and nuts (such as beans, peas, and peanuts), (3) dairy products (such as infant formula, yogurt and cheese), (4) flesh foods (such as chicken, beef, fish, and seafood), (5) eggs, (6) vitamin-A rich fruits and vegetables (such as carrot, pumpkin, and green leafy vegetables), and (7) other fruits and vegetables (such as apple, banana, and pear).

Exclusive breastfeeding was defined as infants being breastfed and no other liquids or foods were given in the last 24 hours. Infants who were exclusively breastfed for at least 6 months were considered to meet the WHO infant feeding recommendations (WHO/UNICEF, 2003). Introduction of complementary foods was defined as infants were given any of the foods listed in the last 24 hours. Infants who were introduced with complementary foods at 6 months were considered to meet the WHO infant feeding recommendations (WHO/UNICEF, 2003). A score of one was given if any foods in a particular food group were consumed in the last 24 hours and a score of zero was given when no foods in a particular food group were consumed. Scores for the seven foods groups were summed to obtain a total score. The total score ranges from 0 to 7, where a higher score indicates a more diverse diet with more food groups being consumed by the infants. The total score was then categorised into two groups, namely, < 4 food groups and ≥ 4 food groups (WHO, 2008). Minimum dietary diversity was defined as infants who received foods from ≥ 4 food groups (WHO, 2008).

3.13.7 Eczema

Eczema in infants was assessed based on the UK Working Party's Diagnostic Criteria for Atopic Dermatitis (Williams et al., 1994). The UK diagnostic criteria have been extensively validated in previous studies, tested in different populations, and demonstrated sensitivity and specificity ranging from 70.0% to 95.5% and 89.3% to 97.5%, respectively (Brenninkmeijer, Schram, Leeflang, Bos, & Spuls, 2008; De, Kanwar, & Handa, 2006; Gu et al., 2001; Jøhnke et al., 2005; Saeki et al., 2007; Williams, Burney, Pembroke, & Hay, 1996). Mothers were asked if their children ever had an itchy skin condition or history of scratching or rubbing that affects the skin creases (fronts of elbows, behind the knees, fronts of ankles, around the neck, around eyes or cheeks), and suffered from a dry skin. In addition, the researchers examined if the infants had any visible flexural eczema on the front of ankles, behind the knees, front of elbows, side or front

of the neck, around the ears or eyes, or cheeks by referring to the reference photograph showed in Deleuran et al. (2006) and Lewis-Jones (2010). The presence of an itchy skin condition (or parental report of scratching or rubbing) plus three or more of the following diagnostic criteria: (1) history of involvement of skin creases such as folds of elbows, behind the knees, front of ankles, cheeks, or around the neck, (2) a history of atopic disease in a first-degree relative, (3) a history of a general dry skin, (4) visible dermatitis affecting the flexures, cheeks/forehead, and outer surface of the limbs, and (5) onset of eczema under the age of 2 years, indicates the presence of eczema (Williams et al., 1994). Infants with eczema at any time point of the follow up within 12 months were defined as "ever had eczema".

3.13.8 Food Allergy

Food allergy in infants was assessed based on convincing clinical history that encompassed three of the following criteria: (i) parent reporting at least one recognized allergic symptom, which included localized symptoms (such as itching, sting/burning of the lips/mouth/throat, urticaria/hives, angioedema), abdominal symptoms (such as nausea, vomiting, crampy/colicky abdominal pain, diarrhea), respiratory symptoms (such as wheeze, stridor, watery rhinitis, redness of eyes/nose), skin symptoms (such as urticaria, itching, flushed skin, worsening eczema), or systemic reactions (such as anaphylaxis, syncope); (ii) parent reporting a temporal relationship of a reaction, with symptoms occurring within 2 h of food ingestion; and (iii) symptoms repeated each time the same food was consumed (Pawankar et al., 2013). Infants with parent-reported food allergy at any time point of the follow up within 12 months were defined as "ever had parent-reported food allergy". Infants with parent-reported food allergy and had a specific IgE level of class ≥ 1 to a specific food allergen (as described in section 3.12.2) were defined as having "IgE-mediated food allergy" (Anvari, Miller, Yeh, & Davis, 2019).

3.14 Data Analysis and Interpretation

Statistical analysis was performed using IBM SPSS Statistics 22 software (IBM SPSS Armonk, NY). In the descriptive analysis, continuous variables were reported as mean and standard deviation, while categorical variables were reported as number and percentages. Chi-square test and Fisher's exact test were used to determine the associations between two or more groups of categorical variables and independent samples t-test was used to compare the mean values of a continuous variable between two groups.

A multivariable generalised linear mixed model (GLMM) was used to determine the associations of maternal vitamin D status during late pregnancy and infant feeding practices with allergic diseases and malnutrition in infants during the first year of life. This statistical method takes into account the clustering effects within study sites and respondents, and able to fit a model using

longitudinal data with unequally spaced repeated outcome measures. First, the associations between the independent variables and with each outcome at 12 months of age were assessed using a binomial distribution with logit link function. Maternal vitamin D status during late pregnancy, exclusive breastfeeding, introduction of complementary foods, and minimum dietary diversity were entered as fixed effect. Health clinics and mother-infant pairs were entered as random effect using the variance component covariance matrix. Allergic diseases (ever had eczema, ever had parent-reported food allergy, IgE-mediated food allergy, and food sensitisation) and malnutrition (stunting, wasting, underweight, and overweight at 12 months) were entered as outcome variables. Two models were created for each outcome variable. The crude model assessed the crude associations between all independent variables with each outcome variable, while the adjusted model assessed the associations between all independent variables with each outcome variable adjusted for potential confounding variables.

Second, an interaction term of each independent variable with time was included in the multivariable GLMM to determine whether the associations between the independent variables and each outcome variable changed with time. Time was coded as time 1 (3 months), 2 (6 months), and 3 (12 months). All independent variables, time, and the interaction term of the independent variables with time were entered as main effect. Health clinics and mother-infant pairs were entered as random effect and time was modelled as a repeated measure. Allergic diseases (eczema and parent-reported food allergy) and malnutrition (WAZ, LAZ, WLZ, BAZ, stunting, wasting, underweight, and overweight) were included as outcome variables in the model. The crude model assessed the unadjusted associations between the independent variables, time, interaction between independent variables with time with each outcome variable and the adjusted model assessed the associations after adjustment of the confounding variables. Model fit was indicated by a lower Bayesian Information Criterion (BIC) values (IBM Corp, 2012).

Multivariable linear mixed model (LMM) were used to examine the associations of maternal vitamin D status during late pregnancy and infant feeding practices with growth indicators in infants during the first year of life. Maternal vitamin D status during late pregnancy, exclusive breastfeeding, introduction of complementary foods, and minimum dietary diversity were entered as fixed effect. Health clinics and mother-infant pairs were entered as random effect. Growth indicators (WAZ, LAZ, WLZ, and BAZ) were entered as outcome variables. Two models were created for each outcome variable. The crude model assessed the crude associations between all independent variables with each outcome variable, while the adjusted model assessed the associations between all independent variables with each outcome variable adjusted for potential confounding variables.

Potential confounding variables were identified from the literature (Nurmatov et al., 2012) and incorporated into a directed acyclic graph (DAG) (Figure 3.4) using DAGitty Version 1.1 (Johannes Textor, Utrecht University, NL). The potential confounding variables for allergic

diseases include maternal characteristics (age, educational level, work status, monthly household income, gestational age at blood withdrawal, maternal antibiotic use in pregnancy), obstetrical history (parity), family history of allergic diseases, infant characteristics (sex, mode of delivery, gestational age at birth, birth weight), and environmental factors (number of siblings, pet at home during the first year, daycare attendance during the first year, and infant antibiotic use during the first year). Allergic diseases in infants including eczema and food allergy were mutually adjusted. Eczema during early life plays an important role in the development of food allergy and may influence maternal infant-feeding decisions. Adjusting infant's eczema status in the food allergy model and vice versa could account for the potential reverse causation (Goldsmith et al., 2016; Lodge et al., 2015; Lowe et al, 2006; Matsumoto et al., 2019). Meanwhile, the potential confounding variables for malnutrition include maternal characteristics (age, ethnicity, educational level, work status, monthly household income, gestational age at blood withdrawal), obstetrical history (parity, pre-pregnancy BMI, gestational weight gain), and infant characteristics (sex, mode of delivery, gestational age at birth, birth weight).

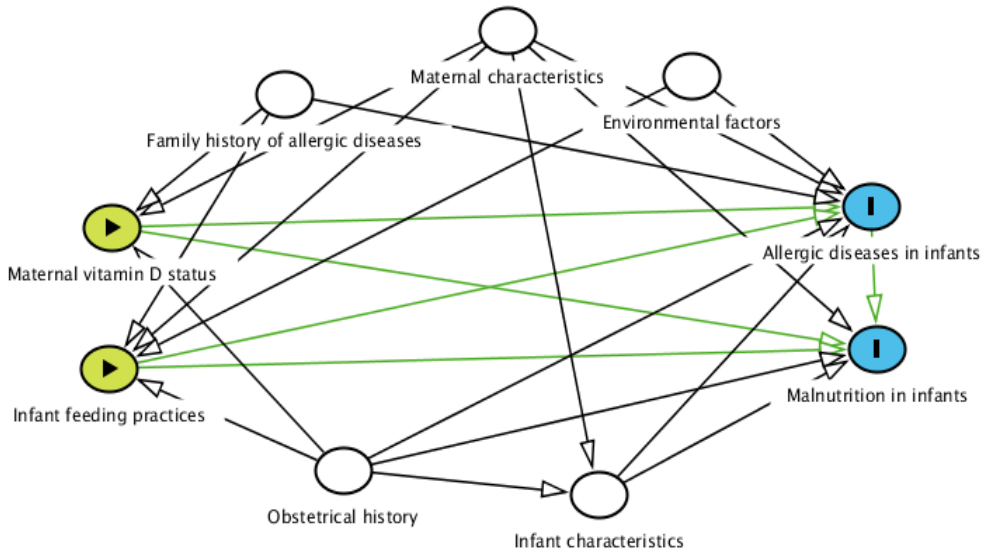


Figure 3.4 Directed acyclic graph

Based on results from the multivariable model, a structural equation model (SEM) was constructed using the IBM SPSS AMOS 22.0 software (Arbuckle, 2013). The Markov chain Monte Carlo (MCMC) algorithm methods were used to obtain Bayesian estimation in SEM as the hypothesized model consisted of dichotomous variables. Convergence statistic less than 1.002 indicates stable estimates of the parameter (Arbuckle, 2014). A Bayesian posterior predictive *p*-value close to 0.50 indicates model fit and a 95% credibility interval (CrI) that does not cover zero indicates significant cross-loading (Muthén & Asparouhov, 2012).

Chapter 4

Results

4.1 Characteristics of the Respondents

Characteristics of the respondents in the present study were illustrated in Table 4.1 Overall, the mean age of the third trimester pregnant women was 29.9 ± 4.1 years old and mean gestational age at blood withdrawal was 32.2 ± 3.6 weeks. Of the 512 pregnant women, majority of them were Malay (92.0%) and a small minority of them were non-Malay including Chinese and Indian (8.0%). About four-fifths of the pregnant women attained tertiary education (81.8%), while about a fifth of them attained secondary education (18.2%). A large proportion of them were working (69.5%). The occupation groups of the pregnant women include professionals (39.5%), technicians and associate professionals (11.1%), service and sales workers (8.4%), clerical support workers (6.6%), managers (2.0%), plant and machine operators (1.8%), and craft and related trade workers (0.2%). About half of them had a moderate monthly household income (52.5%) and were multiparous (57.6%). In terms of pre-pregnancy weight status, about one-third of the pregnant women were overweight or obese (36.9%), and a small proportion of them were underweight (9.2%). While 30.9% of the pregnant women had inadequate weight gain throughout pregnancy, 29.1% had excessive weight during pregnancy. About one in ten of the pregnant women (9.8%) were prescribed with antibiotic medication during pregnancy. The proportion of those with a family history of allergic disease was 66.0%. The mean gestational age at birth for infants was 38.9 ± 1.1 weeks. Out of 430 infants, 73.0% were delivered vaginally and 27.0% were delivered by caesarean. About half of the infants were male (51.4%), while 48.6% were female. The mean birth weight of the infants was 3.1 ± 0.4 kg. More than half of the infants had at least one sibling (58.6%), attended a daycare (54.5%), and were prescribed with antibiotics (58.9%), while a quarter owned a pet at home (24.5%) within their first year of life.

Table 4.1. Characteristics of the respondents

Variable	N	Mean ± SD	n (%)
Third trimester of pregnancy			
Maternal characteristics			
Maternal age (year)	512	29.9 ± 4.1	
Gestational age at blood withdrawal (week)	512	32.2 ± 3.6	
Maternal ethnicity	512		
Malay			471 (92.0)
Non-Malay			41 (8.0)
Maternal educational level	512		
Secondary			93 (18.2)
Tertiary			419 (81.8)
Maternal work status	512		
Working			356 (69.5)
Non-working			156 (30.5)
Monthly household income	512		
Low (< RM 2300)			85 (16.6)
Moderate (RM 2300-5599)			269 (52.5)
High (> RM 5600)			158 (30.9)

Table 4.1. Characteristics of the respondents (continued)

Variable	N	Mean ± SD	n (%)
Maternal antibiotic use during pregnancy	512		
No			462 (90.2)
Yes			50 (9.8)
Obstetrical history			
Parity	512		
Primiparous			217 (42.4)
Multiparous			295 (57.6)
Pre-pregnancy BMI	512		
Underweight (< 18.5 kg/m^2)			47 (9.2)
Normal weight (18.5-24.9 kg/m^2)			276 (53.9)
Overweight/obese (≥ 25.0 kg/m^2)			189 (36.9)
Gestational weight gain	512		
Inadequate			158 (30.9)
Adequate			205 (40.0)
Excessive			149 (29.1)
Family history of allergic disease	512		
No			174 (34.0)
Yes			338 (66.0)
Follow-up at 3 months			
Infant characteristics			
Gestational age at birth (week)	430	38.9 ± 1.1	
Birth weight (kg)	430	3.1 ± 0.4	
Mode of delivery	430		
Vaginal			314 (73.0)
Caesarean			116 (27.0)
Infant sex	430		
Male			221 (51.4)
Female			209 (48.6)
Environmental factors			
Number of siblings	430		
No			178 (41.4)
≥ 1			252 (58.6)
Pet at home	430		
No			352 (81.9)
Yes			78 (18.1)
Daycare attendance	430		
No			246 (57.2)
Yes			184 (42.8)
Infant antibiotic use	430		
No			372 (86.5)
Yes			58 (13.5)
Follow-up at 6 months			
Environmental factors			
Pet at home	406		
No			323 (79.6)
Yes			83 (20.4)
Daycare attendance	406		
No			206 (50.7)
Yes			200 (49.3)
Infant antibiotic use	406		
No			301 (74.1)
Yes			105 (25.9)
Follow-up at 12 months			
Environmental factors			
Pet at home	380		
No			287 (75.5)
Yes			93 (24.5)
Daycare attendance	380		
No			173 (45.5)
Yes			207 (54.5)
Infant antibiotic use	380		
No			156 (41.1)
Yes			224 (58.9)

Note: 1 US dollar = RM 4.09 (as of March 24, 2020)

4.2 Maternal Vitamin D Status during Late Pregnancy

The mean serum vitamin D levels of the pregnant women at the third trimester of pregnancy was 33.9 ± 13.1 nmol/L. The vitamin D level was then classified into three categories based on the IOM (2011) classification. As shown in Table 4.2, 42.8% of the pregnant women were vitamin D deficient and nearly half of them were vitamin D insufficient (48.8%). The pregnant women consumed an average of 10.3 ± 7.9 μg of vitamin D daily, with three-quarters of them did not achieve the RNI for vitamin D (74.4%). Overall, the pregnant women spent about of 4.3 minutes per day being exposed to the sunlight, had a median SEI of 0.6, and exposed 1.1% of their body surface area to the sunlight daily.

Table 4.2. Distribution of respondents according to maternal vitamin D status during late pregnancy and sources of vitamin D (N = 512)

	Mean ± SD / Median (IQR)	n (%)
Maternal vitamin D status (nmol/L)	33.9 ± 13.1	
Deficient (< 30 nmol/L)		219 (42.8)
Insufficient (30-49.9 nmol/L)		250 (48.8)
Sufficient (≥ 50 nmol/L)		43 (8.4)
Dietary vitamin D intake (μg/day)	10.3 ± 7.9	
Below RNI (< 15 μg/day)		381 (74.4)
Above RNI (≥ 15 μg/day)		131 (25.6)
Intake of supplements containing vitamin D		
No		339 (66.2)
Yes		173 (33.8)
Total minutes of sun exposure per day	4.3 (0, 17.1)	
Total % BSA per day	1.1 (0, 5.4)	
SEI per day	0.6 (0, 2.3)	

Note: BSA, Body Surface Area; IQR, Interquartile Range; RNI, Recommended Nutrient Intakes; SEI, Sun Exposure Index

Table 4.3 shows the distribution of maternal vitamin D status by characteristics of the respondents and sources of vitamin D. The proportion of pregnant women with a deficient vitamin D status was significantly higher among Malays as compared to non-Malays (χ^2 = 22.89, p = 0.001). Lower dietary vitamin D intake was significantly associated with vitamin D deficiency in late pregnancy (t = 3.69, p = 0.001). Pregnant women who did not consume supplements containing vitamin D were more likely to have vitamin D deficiency in late pregnancy (χ^2 = 10.31, p = 0.001).

Table 4.3. Distribution of maternal vitamin D status by characteristics of the respondents

Variable	Maternal vitamin D status		
	Deficient (< 30 nmol/L)	Non-deficient (≥ 30 nmol/L)	*p*-value
Maternal characteristics			
Maternal age (year) [a]	29.7 ± 4.0	30.1 ± 4.2	0.337
Gestational age at blood withdrawal (week) [a]	32.4 ± 3.5	32.0 ± 3.6	0.309
Maternal ethnicity			
Malay	216 (45.9)	255 (54.1)	0.001*
Non-Malay	3 (7.3)	38 (92.7)	
Maternal educational level			
Secondary	42 (45.2)	51 (54.8)	0.607
Tertiary	177 (42.2)	242 (57.8)	
Maternal work status			
Working	154 (43.3)	202 (56.7)	0.738
Non-working	65 (41.7)	91 (58.3)	
Monthly household income			
Low (< RM 2300)	41 (48.2)	44 (51.8)	0.107
Moderate (RM 2300-5599)	121 (45.0)	148 (55.0)	
High (> RM 5600)	57 (36.1)	101 (63.9)	
Obstetrical history			
Parity			
Primiparous	90 (41.5)	127 (58.5)	0.610
Multiparous	129 (43.7)	166 (56.3)	
Pre-pregnancy BMI			
Underweight (< 18.5 kg/m^2)	18 (38.3)	29 (61.7)	0.735
Normal weight (18.5-24.9 kg/m^2)	117 (42.4)	159 (57.6)	
Overweight/obese (≥ 25.0 kg/m^2)	84 (44.4)	105 (55.6)	
Gestational weight gain			
Inadequate	66 (41.8)	92 (58.2)	0.702
Adequate	85 (41.5)	120 (58.5)	
Excessive	68 (45.6)	81 (54.4)	
Sources of vitamin D			
Dietary vitamin D intake (μg/day) [a]	8.8 ± 6.8	11.4 ± 8.5	0.001*
Intake of supplements containing vitamin D			
No	162 (47.8)	177 (52.2)	0.001*
Yes	57 (32.9)	116 (67.1)	
Total minutes of sun exposure per day [b]	4.3 (0, 17.1)	7.1 (0, 17.1)	0.685
Total % BSA per day [b]	1.1 (0, 4.3)	1.7 (0, 5.8)	0.135
SEI per day [b]	0.5 (0, 2.1)	0.8 (0, 2.4)	0.443

Note: Data are presented as n (%) and all tests of significance are chi-square test, unless mentioned. *p<0.05. [a] Data are presented as Mean ± SD and test of significance are independent samples t-test. [b] Data are presented as Median (IQR) and test of significance are independent samples t-test.

4.3 Infant Feeding Practices

Infant feeding practices during the first year of life were outlined in Table 4.4. Overall, the duration of exclusive breastfeeding ranged from 1 day to 6.5 months with an average of 3.9 ± 2.3 months. While more than half of the infants were exclusively breastfed for < 6 months (53.4%), 46.6% met the WHO recommendations for being exclusively breastfed until 6 months. It can be observed that complementary feeding was introduced to the infants between 4 to 6.5 months with a mean age of 6.0 ± 0.1 months. A large proportion of the infants complied to the WHO recommendations to receive complementary foods at 6 months of age (97.1%), while only 2.9% of them were introduced to food at less than 6 months of age. At 6 months of age, the infants were given 0 to 5 food groups per day by the mothers and only 10.4% achieved the minimum dietary diversity (MDD). The proportion of infants who achieved the MDD increased to 54.5% at 12 months of age, with 1 to 6 food groups were being introduced to the infants daily.

Table 4.4. Distribution of respondents according to infant feeding practices

Infant feeding practices	Range	Mean ± SD	n (%)
Exclusive breastfeeding (months) (N = 380)	0-6.5	3.9 ± 2.3	
Not met			203 (53.4)
Met			177 (46.6)
Introduction of complementary foods (months) (N = 380)	4.5-6.5	6.0 ± 0.1	
Not met			11 (2.9)
Met			369 (97.1)
Minimum dietary diversity at 6 months (groups) (N = 406)	0-5	1.9 ± 1.1	
Not met			363 (89.4)
Met			43 (10.6)
Minimum diet diversity at 12 months (groups) (N = 380)	1-6	3.6 ± 1.0	
Not met			173 (45.5)
Met			207 (54.5)

Table 4.5 revealed the types of food groups being introduced to the infants at 6 and 12 months of age. Two-third of the infants were introduced with grains, roots, and tubers at 6 months (69.5%), followed by dairy products (46.8%), vitamin A rich fruits and vegetables (37.2%), other fruit and vegetables (20.2%), flesh foods (18.0%), and legumes and nuts (2.2%). The number of infants who were introduced with grains, roots, and tubers have increased to 100.0% at 12 months of age, followed by flesh foods (79.2%), dairy products (66.6%), vitamin A rich fruits and vegetables (64.7%), other fruit and vegetables (32.9%), eggs (10.5%), and legumes and nuts (5.3%). Among those who met the MDD at 6 months, the most common food groups introduced to the infants were grains, roots, and tubers such as plain porridge, commercial infant rice cereals, commercial infant biscuits, and potato (100.0%), vitamin A rich fruits and vegetables such as carrot and broccoli (97.7%), dairy products such as infant formula (90.7%), and flesh foods such as chicken and anchovies (83.7%). On the other hand, the most common food groups introduced to the infants who met the MDD at 12 months were grains, roots, and tubers such as rice, bread, and commercial biscuits (100.0%), flesh foods such as chicken and fish, dairy products such as infant formula (66.6%), and vitamin A rich fruits and vegetables such as carrot, broccoli, and

dark green leafy vegetables.

Table 4.5 Distribution of food groups according to minimum dietary diversity

Food groups	MDD at 6 months (N = 406)			MDD at 12 months (N = 380)		
	Not met n (%)	Met n (%)	Total n (%)	Not met n (%)	Met n (%)	Total n (%)
Grains, roots, tubers	239 (65.8)	43 (100)	282 (69.5)	173 (100)	207 (100)	380 (100)
Dairy products	151 (41.6)	39 (90.7)	190 (46.8)	87 (50.3)	166 (80.2)	253 (66.6)
Vitamin-A rich fruits & vegetables	109 (30.0)	42 (97.7)	151 (37.2)	66 (38.2)	180 (87.0)	246 (64.7)
Other fruits and vegetables	65 (17.9)	17 (39.5)	82 (20.2)	17 (9.8)	108 (52.2)	125 (32.9)
Flesh foods	37 (10.2)	36 (83.7)	73 (18.0)	108 (62.4)	193 (93.2)	301 (79.2)
Eggs	0	0	0	12 (6.9)	28 (13.5)	40 (10.5)
Legumes and nuts	8 (2.2)	1 (2.3)	9 (2.2)	4 (2.3)	16 (7.7)	20 (5.3)

Table 4.6 shows the distribution of infant feeding practices by characteristics of the respondents. Malay mothers were more likely to meet the WHO recommendations to exclusively breastfeed their infant until 6 months ($\chi^2 = 7.07$, $p = 0.008$). Meanwhile, mothers who attained a tertiary educational level ($\chi^2 = 6.74$, $p = 0.009$) and working ($\chi^2 = 10.45$, $p = 0.001$) were more likely to breastfeed their infant until 6 months of age.

4.4 Allergic Diseases in Infants

As shown in Table 4.7, the prevalence of eczema in infants increased from 11.6% at 3 months to 18.2% at 12 months. Similarly, the prevalence of parent-reported food allergy in infants grew from 2.6% at 3 months to 5.9% at 6 months and 18.4% at 12 months, respectively. Overall, it can be seen that the prevalence of eczema and parent-reported food allergy in infants showed a clear upward trend over the first year of life. About 27.6% of the infants had eczema ever and 20.8% of them ever had parent-reported food allergy within the first 12 months of age. Of the 79 cases of parent-reported food allergy, cutaneous symptoms such as hives, skin rashes, itching, or swelling of the lips and eyes were reported by the parents after the infants consumed eggs (8.4%), dairy products (6.8%), shellfish (4.2%), fish (3.2%), chicken (2.1%), specific fruits or vegetables (2.1%), soy products (1.1%), wheat products (0.8%), and tree nuts (0.3%). Of the 314 blood samples collected at 12 months, the serum allergen-specific IgE blood test results showed that 27.4% of the infants were sensitised to at least one food allergen (Table 4.6). The top three food allergens were beef (14.3%), peanut (10.8%), and egg white (7.0%). The prevalence of IgE-mediated food allergy was 3.8%, with 3.2% egg allergy, 1.0% cow's milk allergy, 0.3% soy allergy, and 0.6% wheat allergy.

Table 4.6. Distribution of infant feeding practices by characteristics of the respondents

Variable	Exclusive breastfeeding (N = 380)			Introduction of complementary foods (N = 380) [b]			Minimum dietary diversity at 6 months (N = 406)			Minimum dietary diversity at 12 months (N = 380)		
	No met	Met	*p*-value	No met	Met	*p*-value	No met	Met	*p*-value	No met	Met	*p*-value
Maternal characteristics												
Maternal age (year)[a]	30.2 ± 4.5	29.9 ± 3.8	0.571	28.7 ± 3.6	30.1 ± 4.2	0.263	29.9 ± 4.2	31.2 ± 4.2	0.065	29.9 ± 0.4	30.2 ± 4.1	0.626
Maternal ethnicity												
Malay	189 (51.4)	170 (48.6)	0.008*	9 (2.6)	341 (97.4)	0.213	335 (89.1)	41 (10.9)	0.757[b]	163 (46.6)	187 (53.4)	0.162
Non-Malay	23 (76.7)	7 (23.3)		2 (6.7)	28 (93.3)		28 (93.3)	2 (6.7)		10 (33.3)	20 (66.7)	
Maternal educational level												
Secondary	46 (67.7)	22 (32.4)	0.009*	2 (2.9)	9 (2.9)	1.000	66 (90.4)	7 (9.6)	0.759	27 (39.7)	41 (60.3)	0.287
Tertiary	157 (50.3)	155 (49.7)		9 (2.9)	303 (97.1)		297 (89.2)	36 (10.8)		146 (46.8)	166 (53.2)	
Maternal work status												
Working	157 (58.8)	110 (41.2)	0.001*	9 (3.4)	258 (96.6)	0.518	250 (89.3)	30 (10.7)	0.904	115 (43.1)	152 (56.9)	0.140
Non-working	46 (40.7)	67 (59.3)		2 (1.8)	111 (98.2)		113 (89.7)	13 (10.3)		58 (51.3)	55 (48.7)	
Monthly household income												
Low	30 (57.7)	22 (42.3)	0.388	3 (5.8)	49 (94.2)	0.257	54 (93.1)	4 (6.9)	0.387	28 (53.8)	24 (46.2)	0.360
Moderate	105 (50.2)	104 (49.8)		4 (1.9)	205 (98.1)		200 (90.1)	22 (9.9)		95 (45.5)	114 (54.5)	
High	68 (57.1)	51 (42.9)		4 (3.4)	115 (96.6)		109 (86.5)	17 (13.5)		50 (42.0)	69 (58.0)	
Obstetrical history												
Parity												
Primiparous	91 (59.1)	63 (40.9)	0.067	8 (5.2)	146 (94.8)	0.056	153 (92.2)	13 (7.8)	0.133	67 (43.5)	87 (56.5)	0.514
Multiparous	112 (49.6)	114 (50.4)		3 (1.3)	223 (98.7)		210 (87.5)	30 (12.5)		106 (46.9)	120 (53.1)	
Pre-pregnancy BMI												
Underweight	17 (56.7)	13 (43.3)	0.354	1 (3.3)	29 (96.7)	0.633	32 (97.0)	1 (3.0)	0.310	12 (40.0)	18 (60.0)	0.435
Normal weight	102 (50.0)	102 (50.0)		7 (3.4)	197 (96.6)		194 (88.2)	26 (11.8)		99 (48.5)	105 (51.5)	
Overweight/obese	84 (57.5)	62 (42.5)		3 (2.1)	143 (97.9)		137 (89.5)	16 (10.5)		62 (42.5)	84 (57.5)	
Gestational weight gain												
Inadequate	65 (55.6)	52 (44.4)	0.489	3 (2.6)	114 (97.4)	0.862	115 (90.6)	12 (9.4)	0.623	47 (40.2)	70 (59.8)	0.138
Adequate	75 (49.7)	76 (50.3)		4 (2.6)	147 (97.4)		141 (87.6)	20 (12.4)		78 (51.7)	73 (48.3)	
Excessive	63 (56.3)	49 (43.8)		4 (3.6)	108 (96.4)		107 (90.7)	11 (9.3)		48 (42.9)	64 (57.1)	

Table 4.6. Distribution of infant feeding practices by characteristics of the respondents (continued)

Variable	Exclusive breastfeeding (N = 380)			Introduction of complementary foods (N = 380)			Minimum dietary diversity at 6 months (N = 406)			Minimum dietary diversity at 12 months (N = 380)		
	No met	Met	*p*-value	No met	Met	*p*-value	No met	Met	*p*-value	No met	Met	*p*-value
Family history of allergic disease												
No	62 (50.4)	61 (49.6)	0.415	2 (1.6)	121 (98.4)	0.514	119 (92.2)	10 (7.8)	0.205	56 (45.5)	67 (54.5)	1.000
Yes	141 (54.9)	116 (45.1)		9 (3.5)	248 (96.5)		244 (88.1)	33 (11.9)		117 (45.5)	140 (54.5)	
Infant characteristics												
Gestational age at birth (week)[a]	38.8 ± 1.1	38.9 ± 1.1	0.450	38.4 ± 1.0	38.9 ± 1.1	0.147	38.9 ± 1.1	38.7 ± 1.0	0.285	38.9 ± 1.2	38.8 ± 1.1	0.392
Birth weight (kg)[a]	3.1 ± 0.4	3.1 ± 0.4	0.538	2.9 ± 0.3	3.1 ± 0.4	0.255	3.1 ± 0.4	3.0 ± 0.4	0.338	3.1 ± 0.4	3.1 ± 0.4	0.260
Mode of delivery												
Vaginal	149 (53.6)	129 (46.4)	0.910	6 (2.2)	272 (97.8)	0.174	264 (89.5)	31 (10.5)	0.930	125 (45.0)	153 (55.0)	0.716
Cesarean	54 (52.9)	48 (47.1)		5 (4.9)	97 (95.1)		99 (89.2)	12 (10.8)		48 (47.1)	54 (52.9)	
Infant sex												
Male	98 (51.6)	92 (48.4)	0.472	6 (3.2)	184 (96.8)	1.000	189 (91.7)	17 (8.3)	0.120	84 (44.2)	106 (55.8)	0.607
Female	105 (55.3)	85 (44.7)		5 (2.6)	185 (97.4)		174 (87.0)	26 (13.0)		89 (46.8)	101 (53.2)	

Note: Data are presented as n (%) and all tests of significance are chi-square test, unless mentioned. * $p < 0.05$.
[a]Data are presented as Mean ± SD and test of significance are independent samples t-test.
[b]Fisher's exact test was performed as expected count less than five was more than 20%.

Table 4.7. Prevalence of allergic diseases in infants

Allergic diseases	n (%)
Eczema	
3 months (N = 430)	50 (11.6)
6 months (N = 406)	60 (14.8)
12 months (N = 380)	69 (18.2)
Ever had eczema (N = 380)	105 (27.6)
Parent-reported food allergy	
3 months (N = 430)	11 (2.6)
6 months (N = 406)	24 (5.9)
12 months (N = 380)	70 (18.4)
Ever had food allergy (N = 380)	79 (20.8)
- Eggs (N = 380)	32 (8.4)
- Fish (N = 380)	12 (3.2)
- Shellfish (N = 380)	16 (4.2)
- Cow's milk (N = 380)	26 (6.8)
- Soy (N = 380)	4 (1.1)
- Chicken (N = 380)	8 (2.1)
- Fruits or vegetables (N = 380)	8 (2.1)
- Wheat (N = 380)	3 (0.8)
- Tree nuts (N = 380)	1 (0.3)
Food sensitisation at 12 months	86 (27.4)
Beef (N = 314)	45 (14.3)
Peanut (N = 314)	34 (10.8)
Egg white (N = 314)	22 (7.0)
Egg yolk (N = 314)	10 (3.2)
Soya (N = 314)	14 (4.5)
Cow's milk (N = 314)	7 (2.2)
Shellfish (clam, crab, shrimp) (N = 314)	6 (1.9)
Fish (codfish, tuna, salmon) (N = 314)	4 (1.3)
Wheat (N = 314)	4 (1.3)
Others (rice, orange, chocolate, chicken) (N = 314)	4 (1.3)
IgE-mediated food allergy at 12 months	12 (3.8)
Eggs (N = 314)	10 (3.2)
Cow's milk (N = 314)	3 (1.0)
Soy (N = 314)	1 (0.3)
Wheat (N = 314)	2 (0.6)

Table 4.8 shows the distribution of allergic diseases by characteristics of the respondents. Among the characteristics studied, infants of younger ($t = 2.34$, $p = 0.020$) and primiparous ($\chi^2 = 8.00$, $p = 0.005$) mothers and with no sibling ($\chi^2 = 8.00$, $p = 0.005$) were more likely to have food allergy during the first year of life. Infants born by caesarean section ($\chi^2 = 6.73$, $p = 0.010$) were more likely to be sensitised to food allergens. Infants with antibiotic use during the first year were more likely to have IgE-mediated food allery ($\chi^2 = 5.34$, $p = 0.031$).

Table 4.8. Distribution of allergic diseases by characteristics of the respondents

Variable	Ever had eczema (N = 380)			Ever had parent-reported food allergy (N = 380)			Food sensitisation (N = 314)			IgE-mediated food allergy (N = 314)		
	Yes	No	*p*-value	Yes	No	*p*-value	Yes	No	*p*-value	Yes	No	*p*-value
Maternal characteristics												
Maternal age (year)[a]	30.1 ± 4.0	30.0 ± 4.3	0.876	29.1 ± 3.7	30.3 ± 4.3	0.020*	29.7 ± 3.7	30.0 ± 4.3	0.589	28.0 ± 3.3	30.0 ± 4.1	0.089
Gestational age at blood withdrawal[a]	32.2 ± 3.5	32.4 ± 3.6	0.662	32.8 ± 3.4	32.2 ± 3.6	0.188	32.6 ± 3.6	32.3 ± 3.4	0.569	33.6 ± 3.6	32.3 ± 3.5	0.227
Maternal ethnicity												
Malay	96 (27.4)	254 (72.6)	0.762	76 (21.7)	274 (78.3)	0.129	82 (28.5)	206 (71.5)	0.152	12 (4.2)	276 (95.8)	0.608[b]
Non-Malay	9 (30.0)	21 (70.0)		3 (10.0)	27 (90.0)		4 (15.4)	22 (84.6)		0 (0)	26 (100.0)	
Maternal educational level												
Secondary	18 (26.5)	50 (73.5)	0.813	9 (13,2)	59 (86.8)	0.090	12 (21.1)	45 (78.9)	0.236	1 (1.8)	56 (98.2)	0.701[b]
Tertiary	87 (27.9)	225 (72.1)		70 (22.4)	242 (77.6)		74 (28.8)	183 (71.2)		11 (4.3)	246 (95.7)	
Maternal work status												
Working	70 (26.2)	197 (73.8)	0.343	49 (18.4)	218 (81.6)	0.072	63 (28.9)	155 (71.1)	0.366	8 (3.7)	210 (96.3)	0.761[b]
Non-working	35 (31.0)	78 (69.0)		30 (26.5)	83 (73.5)		23 (24.0)	73 (76.0)		4 (4.2)	92 (95.8)	
Monthly household income												
Low	13 (25.0)	39 (75.0)	0.479	14 (26.9)	38 (73.1)	0.385	10 (21.3)	37 (78.7)	0.491	2 (4.3)	45 (95.7)	0.553[b]
Moderate	63 (30.1)	146 (69.9)		44 (21.1)	165 (78.9)		50 (29.8)	118 (70.2)		8 (4.8)	160 (95.2)	
High	29 (24.4)	90 (75.6)		21 (17.6)	98 (82.4)		26 (26.3)	73 (73.7)		2 (2.0)	97 (98.0)	
Obstetrical history												
Parity												
Primiparous	37 (24.0)	117 (76.0)	0.194	43 (27.9)	111 (72.1)	0.005*	38 (28.1)	97 (71.9)	0.793	8 (5.9)	127 (94.1)	0.135
Multiparous	68 (30.1)	158 (69.9)		36 (15.9)	190 (84.1)		48 (26.8)	131 (73.2)		4 (2.2)	175 (97.8)	
Pre-pregnancy BMI												
Underweight	11 (36.7)	19 (63.3)	0.305	8 (26.7)	22 (73.3)	0.149	6 (24.0)	19 (76.0)	0.914	1 (4.0)	24 (96.0)	0.085[b]
Normal weight	59 (28.9)	145 (71.1)		48 (23.5)	156 (76.5)		49 (28.0)	126 (72.0)		10 (5.7)	165 (94.3)	
Overweight/obese	35 (24.0)	111 (76.0)		23 (15.8)	123 (84.2)		31 (27.2)	83 (72.8)		1 (0.9)	113 (99.1)	
Family history of allergic disease												
No	33 (26.8)	90 (73.2)	0.809	23 (18.7)	100 (81.3)	0.487	33 (32.4)	69 (67.6)	0.171	5 (4.9)	97 (95.1)	0.535
Yes	72 (28.0)	185 (72.0)		56 (21.8)	201 (78.2)		53 (25.0)	159 (75.0)		7 (3.3)	205 (96.7)	

Table 4.8. Distribution of allergic diseases by characteristics of the respondents (continued)

Variable	Ever had eczema (N = 380)			Ever had parent-reported food allergy (N = 380)			Food sensitisation (N =314)			IgE-mediated food allergy (N = 314)		
	Yes	No	*p*-value	Yes	No	*p*-value	Yes	No	*p*-value	Yes	No	*p*-value
Infant characteristics												
Gestational age at birth (week)[a]	38.8 ± 1.1	38.9 ± 1.1	0.780	38.9 ± 1.2	38.8 ± 1.1	0.611	39.0 ± 1.2	38.8 ± 1.1	0.136	39.0 ± 1.5	38.8 ± 1.1	0.694
Birth weight (kg)[a]	3.1 ± 0.4	3.1 ± 0.4	0.716	3.0 ± 0.4	3.1 ± 0.4	0.326	3.1 ± 0.4	3.1 ± 0.4	0.354	3.1 ± 0.5	3.1 ± 0.4	0.981
Mode of delivery												
Vaginal	71 (25.5)	207 (74.5)	0.132	58 (20.9)	220 (79.1)	0.953	53 (23.3)	174 (76.7)	0.010*	8 (3.5)	219 (96.5)	0.743
Cesarean	34 (33.3)	68 (66.7)		21 (20.6)	81 (79.4)		33 (37.9)	54 (62.1)		4 (4.6)	83 (95.4)	
Infant sex												
Male	57 (30.0)	133 (70.0)	0.302	41 (21.6)	149 (78.4)	0.705	45 (27.4)	119 (72.6)	0.983	8 (4.9)	156 (95.1)	0.307
Female	48 (25.3)	142 (74.7)		38 (20.0)	152 (80.0)		41 (27.3)	109 (72.7)		4 (2.7)	146 (97.3)	
Environmental factors												
Maternal antibiotic use during pregnancy												
No	94 (28.0)	242 (72.0)	0.678	72 (21.4)	264 (78.6)	0.396	75 (27.2)	201 (72.8)	0.818	10 (3.6)	266 (96.4)	0.645
Yes	11 (25.0)	33 (75.0)		7 (15.9)	37 (84.1)		11 (28.9)	27 (71.1)		2 (5.3)	36 (94.7)	
Number of siblings												
No	37 (24.0)	117 (76.0)	0.194	43 (27.9)	111 (72.1)	0.005*	38 (28.1)	97 (71.9)	0.793	8 (5.9)	127 (94.1)	0.091
≥ 1	68 (30.1)	158 (69.9)		36 (15.9)	190 (84.1)		48 (26.8)	131 (73.2)		4 (2.2)	175 (97.8)	
Pet at home during the first year												
No	78 (27.2)	209 (72.8)	0.728	57 (19.9)	230 (80.1)	0.433	64 (27.7)	167 (72.3)	0.834	10 (4.3)	221 (95.7)	0.739
Yes	27 (29.0)	66 (71.0)		22 (23.7)	71 (76.3)		22 (26.5)	61 (73.5)		2 (2.4)	81 (97.6)	
Daycare attendance during the first year												
No	51 (29.5)	122 (70.5)	0.461	43 (24.9)	130 (75.1)	0.074	39 (27.5)	103 (72.5)	0.978	5 (3.5)	137 (96.5)	0.801
Yes	54 (26.1)	153 (73.9)		36 (17.4)	171 (82.6)		47 (27.3)	125 (72.7)		7 (4.1)	165 (95.9)	
Infant antibiotic use during the first year												
No	41 (26.3)	115 (73.7)	0.623	28 (17.9)	128 (82.1)	0.255	34 (26.8)	93 (73.2)	0.840	1 (0.8)	126 (99.2)	0.031*
Yes	64 (28.6)	160 (71.4)		51 (22.8)	173 (77.2)		52 (27.8)	135 (72.2)		11 (5.9)	176 (94.1)	

Note: Data are presented as n (%) and all tests of significance are chi-square test, unless mentioned. * $p < 0.05$.

[a]Data are presented as Mean ± SD and test of significance are independent samples t-test.

[b]Fisher's exact test was performed as expected count less than five was more than 20%.

4.5 Malnutrition in Infants

As shown in Table 4.9, the prevalence of stunting in infants increased from 9.3% at 3 months to 16.3% at 12 months. Similarly, the prevalence of underweight increased from 6.3% at 3 months to 11.6% at 12 months. The prevalence of wasting rose from 3.0% at 3 months to 7.6% at 12 months. In contrast, the overweight prevalence has not changed much over the 12 months, ranged from 2.1% at 3 months to 1.8% at 12 months. The present study indicates that the undernutrition problem was more prevalent than the overnutrition problem in infants during the first year of life.

Table 4.9. Prevalence of malnutrition in infants

Allergic diseases	Mean ± SD	n (%)
Stunting (LAZ < -2)		
3 months (N = 430)	-0.61 ± 1.07	40 (9.3)
6 months (N = 406)	-0.62 ± 1.05	37 (9.1)
12 months (N = 380)	-0.92 ± 1.12	62 (16.3)
Underweight (WAZ < -2)		
3 months (N = 430)	-0.60 ± 0.93	27 (6.3)
6 months (N = 406)	-0.65 ± 1.00	30 (7.4)
12 months (N = 380)	-0.78 ± 0.99	44 (11.6)
Wasting (WLZ < -2)		
3 months (N = 430)	-0.13 ± 1.11	13 (3.0)
6 months (N = 406)	-0.28 ± 1.11	18 (4.4)
12 months (N = 380)	-0.44 ± 1.10	29 (7.6)
Overweight (BAZ > 2)		
3 months (N = 430)	-0.35 ± 1.02	9 (2.1)
6 months (N = 406)	-0.40 ± 1.10	8 (2.0)
12 months (N = 380)	-0.34 ± 1.13	7 (1.8)

Table 4.10 presents the distribution of malnutrition by characteristics of the respondents. Infants of mothers with lower educational level ($\chi^2 = 4.58$, $p = 0.032$) and multiparous ($\chi^2 = 5.28$, $p = 0.022$) were more likely to be stunted at 12 months of age. The proportion of underweight were higher among infants of mothers with lower educational level ($\chi^2 = 4.60$, $p = 0.032$), lower household income ($\chi^2 = 10.38$, $p = 0.006$), and multiparous ($\chi^2 = 8.32$, $p = 0.004$) at 12 months of age. Conversely, infants of primiparous mothers were more likely to be overweight ($\chi^2 = 6.04$, $p = 0.014$). The prevalence of stunting in infants was significantly higher for males than for females at 12 months of age ($\chi^2 = 13.03$, $p = 0.001$). Infants with lower birth weight were more likely to be stunted ($t = 2.17$, $p = 0.031$), wasted ($t = 2.65$, $p = 0.008$), and underweight ($t = 2.68$, $p = 0.008$) at 12 months of age.

Table 4.10. Distribution of malnutrition by characteristics of the respondents

Variable	Stunting (LAZ < -2) (N = 380)			Wasting (WLZ < -2) (N = 380)			Underweight (WAZ < -2) (N = 380)			Overweight (BAZ > 2) (N = 380)		
	Yes	No	*p*-value	Yes	No	*p*-value	Yes	No	*p*-value	Yes	No	*p*-value
Maternal characteristics												
Maternal age (year)[a]	30.5 ± 4.8	30.0 ± 4.1	0.325	29.9 ± 4.1	30.1 ± 4.2	0.877	31.1 ± 4.2	29.9 ± 4.2	0.071	27.9 ± 2.7	30.1 ± 4.2	0.165
Gestational age at birth (week)[a]	32.2 ± 3.8	32.4 ± 3.5	0.734	32.7 ± 3.3	32.3 ± 3.6	0.631	32.2 ± 3.9	32.4 ± 3.5	0.978	32.1 ± 3.1	32.4 ± 3.6	0.875
Maternal ethnicity												
Malay	56 (16.0)	294 (84.0)	0.606[b]	27 (7.7)	323 (92.3)	1.000[b]	42 (12.0)	308 (88.0)	0.555[b]	7 (2.0)	343 (98.0)	1.000[b]
Non-Malay	6 (20.0)	24 (80.0)		2 (6.7)	28 (93.3)		2 (6.7)	28 (93.3)		0 (0)	30 (100.0)	
Maternal educational level												
Secondary	17 (25.0)	51 (75.0)	0.032*	6 (8.8)	62 (91.2)	0.683	13 (19.1)	55 (80.9)	0.032*	2 (2.9)	307 (98.4)	0.613[b]
Tertiary	45 (14.4)	267 (85.6)		23 (7.4)	289 (92.6)		31 (9.9)	281 (90.1)		5 (1.6)	66 (97.1)	
Maternal work status												
Working	41 (15.4)	226 (84.6)	0.436	19 (7.1)	248 (92.9)	0.561	26 (9.7)	241 (90.3)	0.085	6 (2.2)	261 (97.8)	0.679[b]
Non-working	21 (18.6)	92 (81.4)		10 (8.8)	103 (91.2)		18 (15.9)	95 (84.1)		1 (0.9)	112 (99.1)	
Monthly household income												
Low	9 (17.3)	43 (82.7)	0.951	5 (9.6)	47 (90.4)	0.234	10 (19.2)	42 (80.8)	0.006*	2 (3.8)	50 (96.2)	0.476[b]
Moderate	33 (15.8)	176 (84.2)		19 (9.1)	190 (90.9)		29 (13.9)	180 (86.1)		3 (1.4)	206 (98.6)	
High	20 (16.8)	99 (83.2)		5 (4.2)	114 (95.8)		5 (4.2)	114 (95.8)		2 (1.7)	117 (98.3)	
Obstetrical history												
Parity												
Primiparous	17 (11.0)	137 (89.0)	0.022*	11 (7.1)	143 (92.9)	0.767	9 (5.8)	145 (94.2)	0.004*	6 (3.9)	148 (96.1)	0.019*[b]
Multiparous	45 (19.9)	181 (80.1)		18 (8.0)	208 (92.0)		35 (15.5)	191 (84.5)		1 (0.4)	225 (99.6)	

Table 4.10. Distribution of malnutrition by characteristics of the respondents (continued)

Variable	Stunting (LAZ < -2) (N = 380)			Wasting (WLZ < -2) (N = 380)			Underweight (WAZ < -2) (N = 380)			Overweight (BAZ > 2) (N = 380)		
	Yes	No	*p*-value	Yes	No	*p*-value	Yes	No	*p*-value	Yes	No	*p*-value
Pre-pregnancy BMI												
Underweight	3 (10.0)	27 (90.0)	0.463	4 (13.3)	26 (86.7)	0.398	3 (10.0)	27 (90.0)	0.746	0 (0)	30 (100.0)	0.696[b]
Normal weight	37 (18.1)	167 (81.9)		16 (7.8)	188 (92.2)		26 (12.7)	178 (87.3)		3 (1.5)	201 (98.5)	
Overweight/obese	22 (15.1)	124 (84.9)		9 (6.2)	137 (93.8)		15 (10.30	131 (89.7)		4 (2.7)	142 (97.3)	
Gestational weight gain												
Inadequate	18 (15.4)	99 (84.6)	0.618	12 (10.3)	105 (89.7)	0.369	14 (12.0)	103 (88.0)	0.550	1 (0.9)	116 (99.1)	0.076[b]
Adequate	28 (18.5)	123 (81.5)		11 (7.3)	140 (92.7)		20 (13.2)	131 (86.8)		1 (0.7)	150 (99.3)	
Excessive	16 (14.3)	96 (85.7)		6 (5.4)	106 (94.6)		10 (8.9)	102 (91.1)		5 (4.5)	107 (95.5)	
Infant characteristics												
Gestational age at delivery (week)[a]	38.9 ± 1.2	38.9 ± 1.1	0.654	38.8 ± 1.2	38.9 ± 1.1	0.621	38.8 ± 1.1	38.9 ± 1.1	0.768	38.9 ± 1.2	38.9 ± 1.1	0.982
Birth weight (kg)[a]	3.0 ± 0.4	3.1 ± 0.4	0.031*	2.9 ± 0.4	3.1 ± 0.4	0.008*	2.9 ± 0.5	3.1 ± 0.4	0.008*	3.1 ± 0.5	3.1 ± 0.4	0.911
Mode of delivery												
Vaginal	45 (16.2)	233 (83.8)	0.911	21 (7.6)	257 (92.4)	0.925	32 (11.5)	246 (88.5)	0.945	4 (1.4)	274 (98.6)	0.391[b]
Caesarean	17 (16.7)	85 (83.3)		8 (7.8)	94 (92.2)		12 (11.8)	90 (88.2)		3 (2.9)	99 (97.1)	
Infant sex												
Male	44 (23.2)	146 (76.8)	0.001*	16 (8.4)	174 (91.6)	0.562	27 (14.2)	163 (85.8)	0.109	4 (2.1)	186 (97.9)	1.000[b]
Female	18 (9.5)	172 (90.5)		13 (6.8)	177 (93.2)		17 (8.9)	173 (91.1)		3 (1.6)	187 (98.4)	

Note: Data are presented as n (%) and all tests of significance are chi-square test, unless mentioned. * $p < 0.05$.
[a]Data are presented as Mean ± SD and test of significance are independent samples t-test.
[b]Fisher's exact test was performed as expected count less than five was more than 20%.

4.6 Bivariate Analysis

This section presents the bivariate analysis to determine the bivariate associations of maternal vitamin D status during late pregnancy and infant feeding practices with allergic diseases and malnutrition in infants.

4.6.1 Bivariate Associations of Maternal Vitamin D Status during Late Pregnancy with Allergic Diseases and Malnutrition in Infants during the First Year of Life

Table 4.11 illustrates the distribution of allergic diseases and malnutrition during the first year of life by maternal vitamin D status during late pregnancy. Infants of mothers with deficient vitamin D levels in late pregnancy were more likely to develop food allergy at 6 months of age ($\chi^2 = 5.64$, $p = 0.017$). No associations were found between maternal vitamin D status with other allergic diseases and malnutrition in infants.

Table 4.11. Distribution of allergic diseases and malnutrition during the first year of life by maternal vitamin D status during late pregnancy

Variable	**Maternal vitamin D status during late pregnancy**		
	Deficient (< 30 nmol/L)	Non-deficient (≥ 30 nmol/L)	*p*-value
Eczema			
3 months (N = 430)	19 (10.1)	31 (12.9)	0.367
6 months (N = 406)	24 (13.6)	36 (15.7)	0.571
12 months (N = 380)	32 (19.5)	37 (17.1)	0.551
Ever had eczema (N = 380)	46 (28.0)	59 (27.3)	0.874
Parent-reported food allergy			
3 months (N = 430)	7 (3.7)	4 (1.7)	0.225[a]
6 months (N = 406)	16 (9.1)	8 (3.5)	0.017*
12 months (N = 380)	33 (20.1)	37 (17.1)	0.456
Ever had food allergy (N = 380)	41 (25.0)	38 (17.6)	0.078
Food sensitisation (N = 314)	41 (30.4)	45 (25.1)	0.303
IgE-mediated food allergy (N = 314)	3 (2.2)	9 (5.0)	0.199
Stunting			
3 months (N = 430)	14 (7.4)	26 (10.8)	0.231
6 months (N = 406)	12 (6.8)	25 (10.9)	0.160
12 months (N = 380)	26 (15.9)	36 (16.7)	0.832
Underweight			
3 months (N = 430)	9 (4.8)	18 (7.5)	0.251
6 months (N = 406)	14 (8.0)	16 (7.0)	0.703
12 months (N = 380)	20 (12.2)	24 (11.1)	0.744
Wasting			
3 months (N = 430)	5 (2.6)	8 (3.3)	0.685
6 months (N = 406)	7 (4.0)	11 (4.8)	0.696
12 months (N = 380)	11 (6.7)	18 (9.3)	0.554
Overweight			
3 months (N = 430)	5 (2.6)	4 (1.7)	0.515[a]
6 months (N = 406)	4 (2.3)	4 (1.7)	0.732[a]
12 months (N = 380)	3 (1.8)	4 (1.9)	1.000[a]

Note: Data are presented as n (%) and all tests of significance are chi-square test.
[a]Fisher's exact test was performed as expected count less than five was more than 20%.

4.6.2 Bivariate Associations of Infant Feeding Practices with Allergic Diseases and Malnutrition in Infants during the First Year of Life

Table 4.12 shows the distribution of allergic diseases and malnutrition during the first year of life by infant feeding practices. The proportion of infants who were underweight at 12 months of age were significantly higher among those who met the WHO recommendations for exclusively breastfed for at least 6 months compared to those who did not meet the recommendations ($\chi^2 = 5.82$, $p = 0.016$). Infants who met the MDD at 6 months were more likely to have food sensitisation compared to those who did not meet the MDD ($\chi^2 = 6.05$, $p = 0.014$). Infants who met the MDD at 12 months were less likely to be stunted at 3 months of age ($\chi^2 = 3.90$, $p = 0.048$). No associations were found between infant feeding practices with eczema, food allergy, wasting, and overweight.

4.7 Multivariable Generalised Linear Mixed Model (GLMM)

Multivariable GLMM was performed to determine the associations of maternal vitamin D status during late pregnancy and infant feeding practices with allergic diseases and malnutrition in infants during the first year of life, respectively. The between- (health clinics) and within-cluster (mother-infant pairs) effects were adjusted in the multivariable GLMM. Confounding variables adjusted in the GLMM for allergic diseases inclue family history of allergic diseases, maternal age, gestational age at blood withdrawal, number of siblings, and mode of delivery. As eczema and food allergy are highly correlated (Lack, 2014; Martin et al., 2015), eczema was included as one of the confounding factors in GLMM for food allergy and food sensitisation apart from the aforementioned confounding factors. Similarly, food allergy was also included in the GLMM for eczema apart from the aforementioned confounding factors. Confounding factors adjusted in GLMM for malnutrition include maternal educational level, monthly household income, gestational age at blood withdrawal, parity, infant's sex, and birth weight. Due to relatively small numbers of respondents with sufficient vitamin D status (8.4%), the sufficient (≥ 50 nmol/L) and insufficient (30-49.9 nmol/L) categories were collapsed to one category (≥30 nmol/L). The largest category for all independent variables was served as the reference group.

4.7.1 Multivariable GLMM of Associations of Maternal Vitamin D Status during Late Pregnancy and Infant Feeding Practices with Allergic Diseases in Infants during the First Year of Life

As shown in Table 4.13, the crude model showed a significant association between MDD at 6 months and risk of food sensitisation at 12 months of age (OR = 2.40, 95% CI = 1.12-5.14). No associations were found between maternal vitamin D status during late pregnancy and infant feeding practices with ever had eczema, ever had parent-reported food allergy, and IgE-mediated food allergy in infants during the first year of life.

Table 4.12. Distribution of allergic diseases and malnutrition by infant feeding practices during the first year of life

Variable	Exclusive breastfeeding			Introduction of complementary foods [a]			MDD at 6 months of age			MDD at 12 months of age		
	Not Met	Met	*p*-value	Not met	Met	*p*-value	Not met	Met	*p*-value	Not met	Met	*p*-value
Eczema												
3 months (N = 430)	25 (12.3)	18 (10.2)	0.510	1 (9.1)	42 (11.4)	1.000	40 (11.0)	6 (14.0)	0.609[a]	16 (9.2)	27 (13.0)	0.245
6 months (N = 406)	28 (13.8)	30 (16.9)	0.393	0 (0)	58 (15.7)	0.385	50 (13.8)	10 (23.3)	0.098	24 (13.9)	34 (16.4)	0.491
12 months (N = 380)	35 (17.2)	34 (19.2)	0.620	0 (0)	69 (18.7)	0.226	60 (17.6)	9 (22.5)	0.451	31 (17.9)	38 (18.4)	0.912
Ever had eczema (N = 380)	51 (25.1)	54 (30.5)	0.242	1 (9.1)	104 (28.2)	0.302	90 (26.5)	15 (37.5)	0.140	46 (26.6)	59 (28.5)	0.678
Parent-reported food allergy												
3 months (N = 430)	4 (2.0)	6 (3.4)	0.524[a]	0 (0)	10 (2.7)	1.000	10 (2.8)	0 (0)	0.609[a]	5 (2.9)	5 (2.4)	1.000[a]
6 months (N = 406)	10 (4.9)	14 (7.9)	0.233	0 (0)	24 (6.5)	1.000	20 (5.5)	4 (9.3)	0.304[a]	12 (6.9)	12 (5.8)	0.649
12 months (N = 380)	34 (16.7)	36 (20.3)	0.368	1 (9.1)	69 (18.7)	0.697	60 (17.6)	10 (25.0)	0.256	29 (16.8)	41 (19.8)	0.446
Ever had food allergy (N = 380)	39 (19.2)	40 (22.6)	0.417	1 (9.1)	78 (21.1)	0.472	68 (20.0)	11 (27.5)	0.269	35 (20.2)	44 (21.3)	0.806
Food sensitisation (N = 314)	49 (29.9)	37 (24.7)	0.301	3 (33.3)	83 (27.2)	0.709	71 (25.3)	15 (45.5)	0.014*	34 (23.3)	52 (31.0)	0.129
IgE-mediated food allergy (N = 314)	5 (3.0)	7 (4.7)	0.455	0 (0)	12 (3.9)	1.000	12 (4.3)	0 (0)	0.623[a]	5 (3.4)	7 (4.2)	0.732
Stunting												
3 months (N = 430)	22 (10.8)	14 (7.9)	0.331	3 (27.3)	33 (8.9)	0.076	32 (8.8)	6 (14.0)	0.269[a]	22 (12.7)	14 (6.8)	0.048*
6 months (N = 406)	15 (7.4)	18 (10.2)	0.337	0 (0)	33 (8.9)	0.609	32 (8.8)	5 (11.6)	0.573[a]	16 (9.2)	17 (8.2)	0.721
12 months (N = 380)	27 (13.3)	35 (19.8)	0.088	3 (27.3)	59 (16.0)	0.397	57 (16.8)	5 (12.5)	0.490	34 (19.7)	28 (13.5)	0.107
Wasting												
3 months (N = 430)	7 (3.4)	4 (2.3)	0.491	0 (0)	11 (3.0)	1.000	10 (2.8)	2 (4.7)	0.369[a]	2 (1.2)	9 (4.3)	0.065
6 months (N = 406)	12 (5.9)	5 (2.8)	0.147	0 (0)	17 (4.6)	1.000	16 (4.4)	2 (4.7)	1.000[a]	8 (4.6)	9 (4.3)	0.897
12 months (N = 380)	11 (5.4)	18 (10.2)	0.082	0 (0)	29 (7.9)	1.000	26 (7.6)	3 (7.5)	1.000[a]	13 (7.5)	16 (7.7)	0.937
Underweight												
3 months (N = 430)	12 (5.9)	10 (5.6)	0.913	1 (9.1)	21 (5.7)	0.486	20 (5.5)	4 (9.3)	0.304[a]	13 (7.5)	9 (4.3)	0.188
6 months (N = 406)	11 (5.4)	15 (8.5)	0.239	0 (0)	26 (7.0)	1.000	28 (7.7)	2 (4.7)	0.757[a]	11 (6.4)	15 (7.2)	0.733
12 months (N = 380)	16 (7.9)	28 (15.8)	0.016*	0 (0)	44 (11.9)	0.624	41 (12.1)	3 (7.5)	0.600[a]	25 (14.5)	19 (9.2)	0.110
Overweight												
3 months (N = 430)	4 (2.0)	4 2.3)	1.000[a]	0 (0)	8 (2.2)	1.000	7 (1.9)	2 (4.7)	0.245[a]	5 (2.9)	3 (1.4)	0.477[a]
6 months (N = 406)	2 (1.0)	5 (2.8)	0.258[a]	0 (0)	7 (1.9)	1.000	8 (2.2)	0 (0)	1.000[a]	4 (2.3)	3 (1.4)	0.707[a]
12 months (N = 380)	4 (2.0)	3 (1.7)	1.000[a]	0 (0)	7 (1.9)	1.000	7 (2.1)	0 (0)	1.000[a]	2 (1.2)	5 (2.4)	0.462

Note: Data are presented as n (%) and all tests of significance are chi-square test, unless mentioned. * $p < 0.05$.

[a]Fisher's exact test was performed as expected count less than five was more than 20%.

Table 4.13. Multivariable GLMM of associations of maternal vitamin D status during late pregnancy and infant feeding practices with allergic diseases in infants during the first year of life

Variable	Allergic diseases during first year of life							
	Ever had eczema (N = 380)		**Ever had parent-reported food allergy (N = 380)**		**Food sensitisation (N = 314)**		**IgE-mediated food allergy (N = 314)**	
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Crude model								
Vitamin D status during pregnancy								
≥ 30nmol/L	1		1		1		1	
< 30 nmol/L	1.04 (0.66-1.64)	0.873	1.60 (0.97-2.65)	0.068	1.33 (0.80-2.22)	0.265	0.66 (0.23-1.88)	0.433
Exclusive breastfeeding								
Not met	1		1		1		1	
Met	1.38 (0.66-1.64)	0.186	1.41 (0.83-2.40)	0.208	0.90 (0.53-1.52)	0.684	1.13 (0.41-3.14)	0.812
Introduction of complementary foods								
Met	1		1		1		1	
Not met	0.31 (0.04-2.43)	0.264	0.44 (0.05-3.63)	0.443	1.29 (0.30-5.58)	0.731	0.55 (0.01-28.42)	0.763
MDD at 6 months								
Not met	1		1		1		1	
Met	1.87 (0.92-3.82)	0.085	1.66 (0.76-3.62)	0.204	2.40 (1.12-5.14)	0.024*	0.52 (0.06-4.38)	0.549
	aOR (95% CI)	***p*-value**	**aOR (95% CI)**	***p*-value**	**aOR (95% CI)**	***p*-value**	**aOR (95% CI)**	***p*-value**
Adjusted model								
Vitamin D status during pregnancy								
≥ 30 nmol/L	1		1		1		1	
< 30 nmol/L	0.85 (0.52-1.40)	0.522	1.76 (1.01-3.05)	0.044*	1.33 (0.78-2.25)	0.289	0.68 (0.25-1.90)	0.465
Exclusive breastfeeding								
Not met	1		1		1		1	
Met	1.19 (0.72-1.99)	0.493	1.45 (0.80-2.60)	0.218	0.82 (0.47-1.42)	0.469	1.12 (0.40-3.12)	0.825
Introduction of complementary foods								
Met	1		1		1		1	
Not met	0.36 (0.04-2.99)	0.345	0.46 (0.05-4.13)	0.487	1.56 (0.36-6.81)	0.552	0.60 (0.01-27.85)	0.795
MDD at 6 months								
Not met	1		1		1		1	
Met	1.56 (0.72-3.36)	0.263	1.68 (0.70-4.00)	0.242	2.31 (1.02-5.20)	0.044*	0.48 (0.06-3.75)	0.484

Note: Health clinics and mother-infant pairs were entered as random effects. Crude model assessed the associations between all independent variables and allergic diseases. Adjusted model assessed the associations between all independent variables and allergic diseases by adjusting the confounding factors (family history of allergic diseases, maternal age, gestational age at blood withdrawal, mode of delivery, and number of siblings). GLMM for eczema was adjusted for the aforementioned confounding factors and parent-reported food allergy. GLMM for food allergy and food sensitisation was adjusted for the aforementioned confounding factors and eczema. *$p < 0.05$

After adjustment of confounding factors, the association between MDD at 6 months and food sensitisation remained significant. Infants who met the MDD at 6 months were 2.31 times more likely to have food sensitisation at 12 months of age as compared to those who did not meet the MDD [Adjusted odds ratio (aOR) = 2.31, 95% CI = 1.02-5.20). The odds of ever had parent-reported food allergy during the first year of life were 1.76 times higher in infants born to mothers with vitamin D deficiency during late pregnancy (aOR = 1.76, 95% CI = 1.01-3.05). The associations of maternal vitamin D status during late pregnancy and infant feeding practices with ever had eczema and IgE-mediated food allergy remained non-significant in the adjusted model.

4.7.2 Multivariable GLMM of Associations of Maternal Vitamin D Status during Pregnancy and Infant Feeding Practices with Malnutrition in Infants during the First Year of Life

As shown in Table 4.14, there were no associations of maternal vitamin D status during late pregnancy and infant feeding practices with malnutrition in infants during the first year of life. The associations remained insignificant after adjustment of confounding factors.

4.7.3 Multivariable LMM of Associations of Maternal Vitamin D Status during Pregnancy and Infant Feeding Practices with Growth Indicators in Infants during the First Year of Life

Table 4.15 shows the associations of maternal vitamin D status during late pregnancy and infant feeding practices with infants' growth indicators during the first year of life. Infants who complied to the WHO recommendations for being exclusively breastfed until 6 months had lower WAZ (B = -0.30; 95% CI = -0.50, -0.09) and LAZ at 12 months of age (B = -0.29; 95% CI = -0.52, -0.06) after adjustment for confounding variables (Table 4.15).

4.7.4 Multivariable GLMM of Associations between Allergic Diseases and Malnutrition in Infants during the First Year of Life

Table 4.16 shows the associations between allergic diseases and malnutrition in infants. The crude model indicates that infants who ever had parent-reported food allergy were at a higher risk to be wasted at 12 months of age (OR = 2.57, 95% CI = 1.19-5.55). This association remained significant after the confounding factors have been adjusted where the odds of being wasted were 2.54 times higher in infants with ever had parent-reported food allergy as compared to their counterparts during the first year of life (aOR = 2.54, 95% CI = 1.15-5.60). In contrast, the odds of underweight were significantly lower in infants with food sensitisation at 12 months of age (OR = 0.35, 95% CI = 0.13-0.93). The association between food sensitisation and underweight was no longer significant after adjustment for the confounding factors.

Table 4.14. Multivariable GLMM of associations of maternal vitamin D status during late pregnancy and infant feeding practices with malnutrition in infants during the first year of life

Variable	Malnutrition during first year of life							
	Stunting (N = 380)		Wasting (N = 380)		Underweight (N = 380)		Overweight (N = 380)	
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Crude model								
Vitamin D status during pregnancy								
≥ 30 nmol/L	1		1		1		1	
< 30 nmol/L	0.96 (0.55-1.68)	0.895	0.84 (0.39-1.78)	0.643	1.12 (0.59-2.10)	0.732	0.99 (0.35-2.85)	0.990
Exclusive breastfeeding								
Not met	1		1		1		1	
Met	1.69 (0.94-3.01)	0.078	1.68 (0.77-3.64)	0.191	1.92 (0.99-3.72)	0.054	0.89 (0.31-2.62)	0.837
Introduction of complementary foods								
Met	1		1		1		1	
Not met	2.58 (0.64-10.48)	0.183	0.42 (0.01-15.32)	0.636	0.31 (0.01-11.08)	0.518	0.68 (0.02-25.50)	0.836
MDD at 6 months								
Not met	1		1		1		1	
Met	0.87 (0.32-2.37)	0.780	1.19 (0.34-4.13)	0.785	0.80 (0.24-2.72)	0.724	0.68 (0.09-4.88)	0.700
	aOR (95% CI)	***p*-value**	**aOR (95% CI)**	***p*-value**	**aOR (95% CI)**	***p*-value**	**aOR (95% CI)**	***p*-value**
Adjusted model								
Vitamin D status during pregnancy								
≥ 30 nmol/L	1		1		1		1	
< 30 nmol/L	0.99 (0.56-1.78)	0.981	0.80 (0.37-1.69)	0.551	0.98 (0.51-1.87)	0.939	1.00 (0.35-2.87)	0.998
Exclusive breastfeeding								
Not met	1		1		1		1	
Met	1.74 (0.94-3.23)	0.079	1.62 (0.74-3.56)	0.225	1.84 (0.93-3.64)	0.082	0.99 (0.33-2.97)	0.991
Introduction of complementary foods								
Met	1		1		1		1	
Not met	3.14 (0.74-13.39)	0.121	0.40 (0.01-13.73)	0.609	0.37 (0.01-10.99)	0.564	0.56 (0.02-20.57)	0.752
MDD at 6 months								
Not met	1		1		1		1	
Met	0.93 (0.33-2.62)	0.884	1.14 (0.33-3.99)	0.835	0.76 (0.22-2.56)	0.651	0.80 (0.11-5.75)	0.822

Note: Health clinics and mother-infant pairs were entered as random effects. Crude model assessed the crude associations between all independent variables and malnutrition. Adjusted model assessed the associations between all independent variables and allergic diseases by adjusting the confounding factors (educational level, monthly household income, gestational age at blood withdrawal, parity, infant's sex, and birth weight). *p < 0.05

Table 4.15. Multivariable LMM of associations of maternal vitamin D status during late pregnancy and infant feeding practices with growth indicators in infants during the first year of life

Variable	Growth indicators during first year of life							
	WAZ (N = 380)		LAZ (N = 380)		WLZ (N = 380)		BAZ (N = 380)	
	B	**95% CI**	**B**	**95% CI**	**B**	**95% CI**	**B**	**95% CI**
Crude model								
Vitamin D status during pregnancy								
≥ 30 nmol/L	1		1		1		1	
< 30 nmol/L	0.08	-0.11, 0.28	-0.02	-0.24, 0.21	0.11	-0.11, 0.33	0.14	-0.09, 0.37
Exclusive breastfeeding								
Not met	1		1		1		1	
Met	-0.30	-0.50, -0.09*	-0.29	-0.52, -0.06*	-0.19	-0.42, 0.04	-0.18	-0.41, 0.06
Introduction of complementary foods								
Met	1		1		1		1	
Not met	-0.39	-0.99, 0.21	-0.51	-1.19, 0.16	-0.20	-0.87, 0.47	-0.13	-0.81, 0.56
MDD at 6 months								
Not met	1		1		1		1	
Met	-0.14	-0.47, 0.18	-0.02	-0.39, 0.35	-0.19	-0.56, 0.17	-0.19	-0.57, 0.18
	B	**95% CI**	**B**	**95% CI**	**B**	**95% CI**	**B**	**95% CI**
Adjusted model								
Vitamin D status during pregnancy								
≥ 30 nmol/L	1		1		1		1	
< 30 nmol/L	0.09	-0.11, 0.28	-0.02	-0.24, 0.21	0.11	-0.11, 0.33	0.14	-0.09, 0.47
Exclusive breastfeeding								
Not met	1		1		1		1	
Met	-0.30	-0.50, -0.09*	-0.29	-0.52, -0.06*	-0.19	-0.42, 0.04	-0.18	-0.41, 0.06
Introduction of complementary foods								
Met	1		1		1		1	
Not met	-0.40	-0.99, 0.21	-0.51	-1.19, 0.16	-0.20	-0.56, 0.17	-0.13	-0.81, 0.56
MDD at 6 months								
Not met	1		1		1		1	
Met	-0.14	-0.47, 0.18	-0.02	-0.39, 0.35	-0.19	-0.56, 0.17	-0.19	-0.57, 0.18

Note: Health clinics and mother-infant pairs were entered as random effects. Crude model assessed the crude associations between all independent variables and growth indicators. Adjusted model assessed the associations between all independent variables and growth indicators by adjusting the confounding factors (maternal age, gestational age at blood withdrawal, gestational weight gain, parity, infant's sex, and birth weight). *p < 0.05. WAZ, Weight-for-age z -scores; LAZ, Length-for-age z-scores; WLZ, Weight-for-length z-scores; BAZ, BMI-for-age z-scores

Table 4.16. Multivariable GLMM of associations between allergic diseases and malnutrition in infants during the first year of life

Variable	Malnutrition at 12 months of age							
	Stunting (N = 380)		Wasting (N = 380)		Underweight (N = 380)		Overweight (N = 380)	
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Crude model								
Ever had eczema								
No	1		1		1		1	
Yes	1.09 (0.59-1.99)	0.787	1.75 (0.82-3.75)	0.148	1.73 (0.90-3.33)	0.100	1.01 (0.32-3.25)	0.981
Ever had parent-reported food allergy								
No	1		1		1		1	
Yes	1.27 (0.67-2.42)	0.469	2.57 (1.19-5.55)	0.016*	1.30 (0.62-2.70)	0.485	1.15 (0.33-3.97)	0.828
IgE-mediated food allergy								
No	1		1		1		1	
Yes	1.57 (0.41-6.02)	0.509	1.17 (0.15-9.16)	0.881	0.68 (0.09-5.24)	0.710	0.72 (0.02-22.50)	0.849
Food sensitisation								
No	1		1		1		1	
Yes	0.86 (0.44-1.67)	0.657	0.54 (0.18-1.61)	0.269	0.35 (0.13-0.93)	0.035*	0.65 (0.16-2.68)	0.547
	aOR (95% CI)	***p*-value**	**aOR (95% CI)**	***p*-value**	**aOR (95% CI)**	***p*-value**	**aOR (95% CI)**	***p*-value**
Adjusted model								
Ever had eczema								
No	1		1		1		1	
Yes	0.97 (0.52-1.81)	0.919	1.64 (0.76-3.52)	0.204	1.49 (0.77-2.91)	0.240	1.07 (0.34-3.42)	0.905
Ever had parent-reported food allergy								
No	1		1		1		1	
Yes	1.51 (0.76-2.99)	0.241	2.54 (1.15-5.60)	0.021*	1.45 (0.67-3.13)	0.340	1.05 (0.30-3.70)	0.939
IgE-mediated food allergy								
No	1		1		1		1	
Yes	1.89 (0.46-7.73)	0.377	1.25 (0.16-9.88)	0.830	0.83 (0.11-6.44)	0.854	0.63 (0.02-19.33)	0.790
Food sensitisation								
No	1		1		1		1	
Yes	0.95 (0.47-1.89)	0.875	0.58 (0.20-1.69)	0.319	0.38 (0.15-1.00)	0.051	0.66 (0.16-2.69)	0.556

Note: Health clinics and mother-infant pairs were entered as random effects. Crude model assessed the crude associations of each allergic disease with malnutrition, respectively. Adjusted model assessed the associations of each allergic disease and malnutrition by adjusting the confounding factors (educational level, monthly household income, parity, infant's sex, and birth weight). *$p < 0.05$

4.7.5 Multivariable GLMM of associations of maternal vitamin D status during late pregnancy and infant feeding practices with allergic diseases in infants from 3 months to 12 months of age

Associations of maternal vitamin D status during late pregnancy and infant feeding practices with the development of allergic diseases from 3 months to 12 months of age were assessed using a multivariable GLMM. The interaction effects of all independent variables and time on allergic diseases were shown in Table 4.17. Introduction of complementary foods was excluded from the eczema model to improve model fit. Both the crude and adjusted model for eczema showed that there was no time effect and the interactions between all independent variables and time were not statistically significant. Introduction of complementary foods and MDD at 6 months were excluded from the parent-reported food allergy model to improve model fit. Both the crude and adjusted model for parent-reported food allergy showed that there is a significant time effect at 12 months (aOR = 16.68, 95% CI = 4.22-65.95). In other words, there is an increasing prevalence of parent-reported food allergy in infants for both groups of maternal vitamin D status (< 30 and ≥ 30 nmol/L) and exclusive breastfeeding (Met and Not met) at 12 months of age. However, the associations of maternal vitamin D status and exclusive breastfeeding with parent-reported food allergy in infants from 3 to 12 months of age were not significant.

4.7.6 Multivariable GLMM of associations of maternal vitamin D status during late pregnancy and infant feeding practices with malnutrition in infants from 3 months to 12 months of age

Associations of maternal vitamin D status during late pregnancy and infant feeding practices with the development of malnutrition in infants from 3 to 12 months of age were assessed using a multivariable GLMM. The interaction effects of all independent variables and time on malnutrition was shown in Table 4.18. Introduction of complementary foods was excluded from the stunting, wasting, and underweight model, while introduction of complementary foods and MDD at 6 months were excluded from the overweight model to improve model fit. Results showed that there was no significant time effect and the associations of maternal vitamin D status during late pregnancy and infant feeding practices with malnutrition in infants did not change over time.

4.7.7 Multivariable LMM of associations of maternal vitamin D status during late pregnancy and infant feeding practices with growth indicators in infants from 3 months to 12 months of age

Table 4.19 presents the interaction effects of all independent variables and time on growth indicators. A significant interaction between exclusive breastfeeding and time was observed for growth indicators. Infants who complied to the WHO recommendations for being exclusively breastfed until 6 months had lower LAZ (B = -0.18; 95% CI = -0.30, -0.01) and WAZ at 6 months of age (B = -0.31; 95% CI = -0.51, -0.11) after adjustment for confounding variables. At 12 months of age,

Table 4.17. Multivariable GLMM of associations of maternal vitamin D status during late pregnancy and infant feeding practices with allergic diseases in infants from 3 months to 12 months of age

Variable	Crude model for allergic diseases				Adjusted model for allergic diseases			
	Eczema [a]		Parent-reported food allergy		Eczema [a]		Parent-reported food allergy	
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**	**aOR (95% CI)**	***p*-value**	**aOR (95% CI)**	***p*-value**
Vitamin D status during pregnancy [c]								
< 30 nmol/L	0.84 (0.44-1.61)	0.596	2.09 (0.65-6.79)	0.219	0.81 (0.42-1.57)	0.536	2.39 (0.63-9.01)	0.199
Exclusive breastfeeding [d]								
Met	0.84 (0.43-1.63)	0.605	1.98 (0.61-6.44)	0.256	0.72 (0.37-1.42)	0.345	2.28 (0.63-8.98)	0.199
Introduction of complementary foods [e]								
Not met	-		-		-		-	
MDD at 6 months of age [f]								
Met	1.37 (0.52-3.59)	0.525	-		1.22 (0.46-3.28)	0.688	-	
Time [f]								
6 months	1.04 (0.50-2.18)	0.919	2.09 (0.50-8.66)	0.310	1.03 (0.49-2.16)	0.942	2.13 (0.49-9.30)	0.316
12 months	1.26 (0.62-2.58)	0.523	13.41 (3.87-46.50)	0.001*	0.93 (0.44-1.97)	0.847	16.68 (4.22-65.95)	0.001*
Vitamin D status during pregnancy*Time [c,f]								
< 30 nmol/L*6 months	0.93 (0.39-2.22)	0.864	1.41 (0.33-5.94)	0.644	0.86 (0.36-2.04)	0.724	1.46 (0.32-6.61)	0.626
< 30 nmol/L*12 months	1.40 (0.61-3.25)	0.429	0.60 (0.17-2.19)	0.439	1.30 (0.55-3.10)	0.550	0.52 (0.12-2.2)	0.375
Exclusive breastfeeding*Time [d,f]								
Met*6 months	1.74 (0.72-4.24)	0.221	0.97 (0.23-4.02)	0.962	1.56 (0.64-3.78)	0.328	0.90 (0.20-4.03)	0.890
Met*12 months	1.44 (0.61-3.41)	0.402	0.72 (0.20-2.62)	0.619	1.39 (0.57-3.36)	0.472	0.65 (0.15-2.75)	0.557
Introduction of complementary foods*Time [e,f]								
Not Met*6 months	-		-		-		-	
Not met*12months	-		-		-		-	
MDD at 6 months of age*Time [d,f]								
Met*6 months	1.72 (0.49-6.09)	0.401	-		1.50 (0.42-5.39)	0.534	-	
Met*12 months	1.06 (0.30-3.77)	0.929	-		0.94 (0.25-3.54)	0.926	-	

Note: Health clinics and mother-infant pairs were entered as random effects. Crude model assessed the associations between all independent variables and allergic diseases. Adjusted model assessed the associations between all independent variables and allergic diseases by adjusting the confounding factors (maternal age, gestational age at blood withdrawal, family history of allergic diseases, mode of delivery, and number of siblings). GLMM for eczema was adjusted for the aforementioned confounding factors and parent-reported food allergy at 3, 6, and 12 months. GLMM for parent-reported food allergy was adjusted for the aforementioned confounding factors and eczema at 3, 6, and 12 months. *p < 0.05

[a] Introduction of complementary foods was excluded from the eczema model to improve model fit.

[b] Introduction of complementary foods and MDD at 6 months were excluded from the parent-reported food allergy model to improve model fit.

[c] Reference category = ≥ 30 nmol/L

[d] Reference category = Not met

[e] Reference category = Met

[f] Reference category = time 3 months

Table 4.18. Multivariable of associations of maternal vitamin D status during late pregnancy and infant feeding practices with malnutrition in infants from 3 months to 12 months of age

Variable	Crude model for malnutrition							
	Stunting		Wasting		Underweight		Overweight[b]	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Vitamin D status during pregnancy [c]								
< 30 nmol/L	0.62 (0.30-1.29)	0.202	0.73 (0.21-2.55)	0.624	0.74 (0.30-1.81)	0.505	1.33 (0.33-5.44)	0.691
Exclusive breastfeeding [d]								
Met	0.75 (0.36-1.56)	0.446	0.70 (0.19-2.52)	0.586	1.06 (0.43-2.64)	0.893	1.16 (0.28-4.74)	0.837
Introduction of complementary foods [e]								
Not met	-		-		-		-	
MDD at 6 months of age [d]								
Met	1.69 (0.63-4.49)	0.296	1.74 (0.35-8.74)	0.501	2.05 (0.62-6.72)	0.238	-	
Time [f]								
6 months	0.63 (0.27-1.50)	0.295	1.84 (0.54-6.31)	0.330	0.83 (0.28-2.44)	0.739	0.56 (0.08-4.1)	0.571
12 months	1.21 (0.57-2.57)	0.613	1.66 (0.49-5.61)	0.418	1.37 (0.52-3.64)	0.527	1.15 (0.21-6.42)	0.870
Vitamin D status during pregnancy*Time [c,f]								
< 30 nmol/L*6 months	1.03 (0.36-2.97)	0.958	1.23 (0.25-6.08)	0.797	1.85 (0.55-6.19)	0.316	0.76 (0.10-6.07)	0.797
< 30 nmol/L*12 months	1.54 (0.61-3.85)	0.361	1.10 (0.25-4.81)	0.901	1.54 (0.51-4.66)	0.443	0.74 (0.09-5.87)	0.775
Exclusive breastfeeding*Time [d,f]								
Met*6 months	2.06 (0.72-5.91)	0.178	0.65 (0.12-3.49)	0.615	1.49 (0.44-5.10)	0.521	2.52 (0.29-22.3)	0.405
Met*12 months	2.08 (0.83-5.24)	0.119	2.91 (0.64-13.29)	0.168	2.01 (0.65-6.21)	0.224	0.74 (0.09-5.88)	0.776
Introduction of complementary foods*Time [e,f]								
Not Met*6 months	-		-		-		-	
Not met*12months	-		-		-		-	
MDD at 6 months of age*Time [d,f]								
Met*6 months	1.12 (0.26-4.80)	0.878	0.52-0.06-4.85)	0.564	0.40 (0.06-2.78)	0.356	-	
Met*12 months	0.50 (0.12-2.03)	0.330	0.74 (0.09-5.89)	0.775	0.386 (0.07-2.18)	0.281	-	

Note: Health clinics and mother-infant pairs were entered as random effects. Crude model assessed the crude associations of each allergic disease with malnutrition, respectively. *p < 0.05

[a] Introduction of complementary foods was excluded from the stunting, wasting, and underweight model to improve model fit.

[b] Introduction of complementary foods and MDD at 6 months were excluded from the overweight model to improve model fit.

[c] Reference category = ≥ 30 nmol/L

[d] Reference category = Not met

[e] Reference category = Met

[f] Reference category = time 3 months

Table 4.18. Multivariable GLMM of associations of maternal vitamin D status during late pregnancy and infant feeding practices with malnutrition in infants from 3 months to 12 months of age (continued)

Variable	Adjusted model for malnutrition							
	Stunting[a]		Wasting[a]		Underweight[a]		Overweight[b]	
	aOR (95% CI)	*p*-value	aOR (95% CI)	*p*-value	aOR (95% CI)	*p*-value	aOR (95% CI)	*p*-value
Vitamin D status during late pregnancy								
< 30 nmol/L	0.59 (0.30-1.17)	0.128	0.66 (0.19-2.32)	0.514	0.61 (0.25-1.49)	0.277	1.29 (0.35-4.83)	0.704
Exclusive breastfeeding								
Met	0.72 (0.36-1.42)	0.339	0.69 (0.19-2.51)	0.574	0.99 (0.41-2.40)	0.981	1.40 (0.37-5.29)	0.619
Introduction of complementary foods								
Not met	-		-		-		-	
MDD at 6 months of age								
Met	1.86 (0.75-4.62)	0.182	1.76 (0.35-8.96)	0.496	2.11 (0.66-6.75)	0.207	-	
Time [f]								
6 months	0.59 (0.24-1.45)	0.252	1.85 (0.54-6.29)	0.326	0.80 (0.29-2.25)	0.671	0.56 (0.07-4.86)	0.598
12 months	1.23 (0.56-2.68)	0.604	1.66 (0.49-5.68)	0.417	1.37 (0.50-3.76)	0.538	1.16 (0.25-5.34)	0.850
Vitamin D status during late pregnancy*Time [c,f]								
< 30 nmol/L*6 months	1.07 (0.37-3.11)	0.908	1.24 (0.25-6.10)	0.793	1.98 (0.62-6.35)	0.248	0.76 (0.08-7.10)	0.810
< 30 nmol/L*12 months	1.64 (0.65-4.14)	0.297	1.13 (0.25-5.04)	0.872	1.66 (0.53-5.17)	0.382	0.73 (0.12-4.62)	0.741
Exclusive breastfeeding*Time [d,f]								
Met*6 months	2.22 (0.77-6.43)	0.141	0.66 (0.13-3.46)	0.620	1.60 (0.50-5.16)	0.433	2.56 (0.24-27.06)	0.435
Met*12 months	2.25 (0.89-5.72)	0.087	2.98 (0.65-13.67)	0.160	2.19 (0.69-6.90)	0.181	0.73 (0.12-4.62)	0.741
Introduction of complementary foods*Time [e,f]								
Not Met*6 months	-		-		-		-	
Not met*12months	-		-		-		-	
MDD at 6 months of age*Time [d,f]								
Met*6 months	1.14 (0.27-4.95)	0.857	0.52 (0.58-4.73)	0.561	0.37 (0.06-2.29)	0.287	-	
Met*12 months	0.47 (0.11-1.96)	0.300	0.70 (0.09-5.61)	0.735	0.34 (0.06-2.05)	0.240	-	

Note: Health clinics and mother-infant pairs were entered as random effects. Adjusted model assessed the associations of each allergic disease and malnutrition by adjusting the confounding factors (educational level, monthly household income, gestational age at blood withdrawal, parity, infant's sex, and birth weight). *p < 0.05

[a] Introduction of complementary foods was excluded from the stunting, wasting, and underweight model to improve model fit.

[b] Introduction of complementary foods and MDD at 6 months were excluded from the overweight model to improve model fit.

[c] Reference category = ≥ 30 nmol/L

[d] Reference category = Not met

[e] Reference category = Met

[f] Reference category = time 3 months

Table 4.19. Multivariable GLMM of associations of maternal vitamin D status during late pregnancy and infant feeding practices with growth indicators in infants from 3 months to 12 months of age

Variable	Crude model for growth indicators							
	WAZ		LAZ		WLZ		BAZ	
	B	95% CI	B	95% CI	B	95% CI	B	95% CI
Vitamin D status during late pregnancy								
< 30 nmol/L	0.07	-0.12, 0.27	-0.03	-0.25, 0.19	0.14	-0.09, 0.37	0.13	-0.09, 0.36
Exclusive breastfeeding								
Met	0.05	-0.15, 0.25	-0.01	-0.29, 0.16	0.13	-0.10, 0.37	0.13	-0.10, 0.35
Introduction of complementary foods								
Not met	-0.30	-0.89, 0.29	-0.44	-0.52, 0.20	0.04	-0.66, 0.74	-0.07	-0.75, 0.60
MDD at 6 months of age								
Met	-0.19	-0.51, 0.12	-0.16	-0.20, 0.19	-0.07	-0.45, 0.31	-0.13	-0.50, 0.23
Time [f]								
6 months	0.04	-0.06, 0.14	0.13	-0.04, 0.30	-0.15	-0.34, 0.04	-0.04	-0.20, 0.13
12 months	0.00	-0.10, 0.11	-0.18	-0.35, -0.00	-0.15	-0.34, 0.04	0.15	-0.02, 0.31
Vitamin D status during late pregnancy*Time [a]								
< 30 nmol/L*6 months	0.00	-0.12, 0.12	0.12	-0.08, 0.31	-0.07	-0.29, 0.14	-0.08	-0.26, 0.11
< 30 nmol/L*12 months	0.02	-0.10, 0.13	-0.001	-0.20, 0.19	-0.03	-0.25, 0.19	0.01	-0.18, 0.20
Exclusive breastfeeding*Time [b]								
Met*6 months	-0.18	-0.30, -0.07*	-0.31	-0.51, -0.11*	-0.00	-0.22, 0.22	-0.01	-0.20, 0.19
Met*12 months	-0.37	-0.49, -0.26*	-0.23	-0.44, -0.03*	-0.34	-0.57, -0.12*	-0.32	-0.52, -0.13*
Introduction of complementary foods*Time [c]								
Not Met*6 months	0.14	-0.21, 0.49	-0.15	-0.74, 0.45	0.22	-0.43, 0.88	0.31	-0.26, 0.89
Not met*12months	-0.09	-0.44, 0.26	-0.08	-0.67, 0.52	-0.24	-0.89, 0.42	-0.06	-0.63, 0.52
MDD at 6 months of age*Time [d]								
Met*6 months	-0.02	-0.21, 0.17	-0.001	-0.33, 0.32	-0.08	-0.44, 0.28	-0.03	-0.34, 0.28
Met*12 months	0.07	-0.13, 2.57	0.17	-0.16, 0.49	-0.13	-0.49, 0.22	-0.06	-0.38, 0.25

Note: Health clinics and mother-infant pairs were entered as random effects. WAZ, Weight-for-age z -scores; LAZ, Length-for-age z-scores; WLZ, Weight-for-length z-scores; BAZ, BMI-for-age z-scores. *p < 0.05

[a] Reference category = ≥ 30 nmol/L

[b] Reference category = Not met

[c] Reference category = Met

[d] Reference category = time 3 months

Table 4.19. Multivariable GLMM of associations of maternal vitamin D status during late pregnancy and infant feeding practices with growth indicators in infants from 3 months to 12 months of age (continued)

Variable	Adjusted model for growth indicators							
	WAZ		LAZ		WLZ		BAZ	
	B	95% CI	B	95% CI	B	95% CI	B	95% CI
Vitamin D status during late pregnancy								
< 30 nmol/L	0.07	-0.12, 0.27	-0.03	-0.25, 0.19	0.14	-0.09, 0.37	0.13	-0.09, 0.36
Exclusive breastfeeding								
Met	0.05	-0.15, 0.25	-0.06	-0.29, 0.16	0.13	-0.10, 0.37	0.13	-0.10, 0.35
Introduction of complementary foods								
Not met	-0.30	-0.89, 0.29	-0.44	-1.10, 0.27	0.04	-0.66, 0.74	-0.07	-0.75, 0.60
MDD at 6 months of age								
Met	-0.19	-0.51, 0.12	-0.16	-0.52, 0.20	-0.07	-0.45, 0.31	-0.13	-0.50, 0.23
Time [f]								
6 months	0.04	-0.06, 0.14	0.13	-0.04, 0.30	-0.15	-0.34, 0.04	-0.04	-0.20, 0.13
12 months	-0.001	-0.10, 0.11	-0.18	-0.35, -0.004	-0.15	-0.34, 0.05	0.15	-0.02, 0.31
Vitamin D status during late pregnancy*Time [a]								
< 30 nmol/L*6 months	0.02	-0.10, 0.13	0.12	-0.08, 0.31	-0.07	-0.30, 0.14	-0.08	-0.26, 0.11
< 30 nmol/L*12 months	-0.001	-0.12, 0.12	-0.001	-0.20, 0.19	-0.03	-0.25, 0.19	0.01	-0.18, 0.20
Exclusive breastfeeding*Time [b]								
Met*6 months	-0.18	-0.30, -0.01*	-0.31	-0.51, -0.11*	-0.001	-0.22, 0.22	-0.01	-0.20, 0.19
Met*12 months	-0.37	-0.49, -0.26*	-0.23	-0.44, -0.03*	-0.34	-0.57, -0.12*	-0.32	-0.52, -0.13*
Introduction of complementary foods*Time [c]								
Not Met*6 months	0.14	-0.21, 0.49	-0.15	-0.74, 0.45	0.22	-0.43, 0.88	0.31	-0.26, 0.89
Not met*12months	-0.09	-0.44, 0.26	-0.08	-0.67, 0.52	-0.24	-0.89, 0.42	-0.06	-0.63, 0.52
MDD at 6 months of age*Time [d]								
Met*6 months	-0.02	-0.22, 0.17	-0.001	-0.33, 0.32	-0.08	-0.44, 0.28	-0.03	-0.34, 0.28
Met*12 months	0.06	-0.13, 0.26	0.17	-0.16, 0.49	-0.13	-0.49, 0.22	-0.06	-0.38, 0.25

Note: Health clinics and mother-infant pairs were entered as random effects. Adjusted model assessed the associations of each allergic disease and growth indicators by adjusting the confounding factors (maternal age, gestational age at blood withdrawal, gestational weight gain, parity, infant's sex, and birth weight). *p < 0.05

WAZ, Weight-for-age z -scores; LAZ, Length-for-age z-scores; WLZ, Weight-for-length z-scores; BAZ, BMI-for-age z-scores

[a] Reference category = ≥ 30 nmol/L

[b] Reference category = Not met

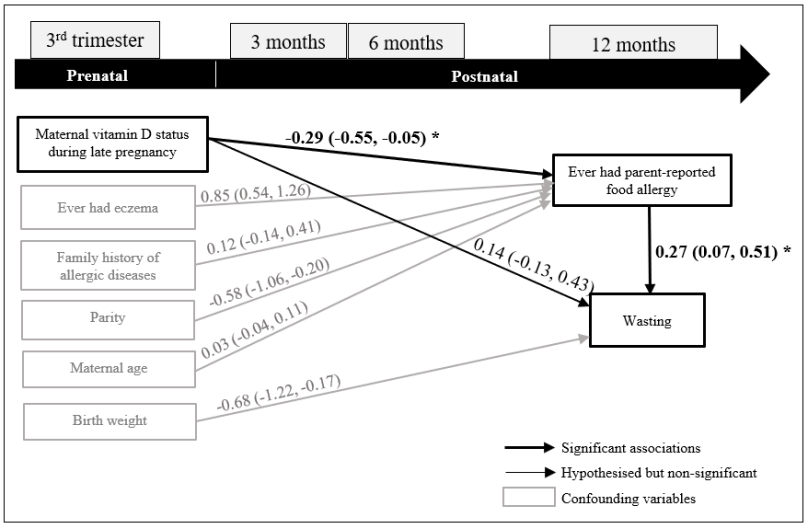
[c] Reference category = Met

[d] Reference category = time 3 months

lower WAZ (B = -0.37, 95% CI = -0.49, -0.26), LAZ (B = -0.23, 95% CI = -0.44, -0.03), WLZ (B = -0.34, 95% CI = -0.57, -0.12), and BAZ (B = -0.32, 95% CI = -0.52, -0.13) were found among infants who were exclusively breastfeed until 6 months of age.

4.8 SEM of Interrelationships between Maternal Vitamin D Status during Late Pregnancy, Parent-reported Food Allergy, and Wasting in Infants during the First Year of Life

The interrelationships between maternal vitamin D status during late pregnancy, ever had parent-reported food allergy, and wasting in infants during the first year of life were assessed using a SEM (Figure 4.1). The SEM was designed based on results from the multivariable GLMM. The independent variable was maternal vitamin D status during late pregnancy and the dependent variables were ever had parent-reported food allergy and wasting. The confounding variables included in the model were based on results from the bivariate analysis between characteristics of the respondents with allergic diseases and malnutrition, namely maternal age and parity (for parent-reported food allergy) and birth weight (for wasting). Family history of allergic diseases and ever had eczema were also included as confounding variables for parent-reported food allergy as previous evidence has demonstrated that they are important predictors of food allergy in early childhood. The SEM model (Figure 4.1) exhibited a good fit with a posterior predictive p-value of 0.52. The SEM model indicated that maternal vitamin D deficiency during late pregnancy was associated with a higher risk of ever had parent-reported food allergy in infants during the first year of life (-0.29, 95% CrI = -0.55, -0.05). Meanwhile, infants who ever had parent-reported food allergy were associated with an increased risk of wasting during the first year of life (0.27, 95% CrI = 0.07, 0.51). No association was found between maternal vitamin D status during late pregnancy and wasting in infants. In other words, the relationship between maternal vitamin D status during late pregnancy and wasting in infants was fully mediated by ever had parent-reported food allergy.



Note: Path coefficients are standardised regression weight and 95% credibility interval. Posterior predictive *p*-value = 0.52

Figure 4.1. SEM of interrelationships between maternal vitamin D status during late pregnancy, food allergy, and wasting in infants during the first year of life.

Chapter 5

Discussion

5.1 Characteristics of the Study Respondents

In the present study, a total of 512 third-trimester pregnant women who attended the selected government health clinics in the state of Selangor and Federal Territory of Kuala Lumpur, Malaysia were recruited. The government health clinics are the primary source providing regular antenatal care to pregnant women in Malaysia. A higher proportion of pregnant women in the present study were Malays (92.0%), attained tertiary education (81.8%), 69.5% were working mothers, 52.5% had a moderate household income, and 57.6% were multiparous. Similarly, in a cross-sectional study conducted by Yeoh et al. (2015) among 522 pregnant women recruited from six government health clinics in Selangor, the majority were Malays (75.9%), 61.9% were employed, and 62.6% were multiparous. Another study conducted among 199 pregnant women recruited from 45 urban health clinics in Selangor reported that majority of the respondents were Malays (72.9%), attained tertiary education (62.8%), had a moderate monthly household income (52.8%) and were employed (71.4%) (Kaur et al., 2019). In terms of infant's characteristics, majority of the infants in the present study were born by vaginal deliveries (73.0%) with a mean birth weight of 3.1 kg. Infant's characteristics in the present study are comparable to the national survey that reported a mean birth weight of 3.1 kg and a higher proportion of vaginal deliveries (61.0%) among infants in Selangor and Kuala Lumpur, (IPH, 2016).

Overall, characteristics of the respondents in the present study were in line with previous studies except with a significantly higher proportion of Malays and higher educational level among the respondents. This indicates that Malay pregnant women were more likely to use the antenatal care services of the government-funded health clinics than other ethnicities, consistent with the findings of the national survey that reported a higher proportion of Malay pregnant women used public health facilities and a higher proportion of Chinese and Indians used private health facilities (IPH, 2016). In addition, the present study indicated that a higher proportion of pregnant women with tertiary educational level were more likely to continue their antenatal care visits during the third trimester of pregnancy. This is consistent with previous studies that the frequency of antenatal care visits was significantly higher among pregnant women with higher educational attainment (IPH, 2016; Yeoh, Hornetz, & Dahlui, 2016).

5.2 Prevalence of Maternal Vitamin D Deficiency During Late Pregnancy

The present study showed that the prevalence of low vitamin D levels was high among pregnant women in their third trimester of pregnancy, whereby almost half of them were vitamin D insufficient (48.8%) and 42.8% had vitamin D deficiency. The combined prevalence of vitamin D

insufficiency and deficiency in the present study (91.6%) was high when compared to the prevalence reported in other tropical countries among the third-trimester pregnant women using the IOM classification for vitamin D status (Aji, Yerizel, Desmawati, & Lipoeto, 2018; Arora et al., 2018; Jan Mohamed et al., 2014; Lee et al., 2017; Pratumvinit et al., 2015). A study conducted in Kuala Lumpur, Malaysia reported that the prevalence of vitamin D insufficiency and deficiency among 575 third trimester pregnant women was 71.7% (Lee et al., 2017). Another study conducted among 102 pregnant women in Kelantan state, Malaysia reported 37.0% prevalence of vitamin D insufficiency (Jan Mohamed et al., 2014). Arora et al., (2018) revealed that 86.0% of Indian pregnant women were vitamin D insufficient and deficient at the time of delivery. In contrast, one-third pregnant women (34.0%) in Thailand (Pratumvinit et al., 2015) and 20.0% pregnant women in Indonesia (Aji et al., 2018) had vitamin D insufficiency and deficiency.

The high prevalence of low vitamin D levels reported in the present study can be explained by the low vitamin D consumption in pregnant women and ethnic disparities (Woon et al., 2019). The pregnant women in the present study consumed a low vitamin D diet, whereby the average vitamin D intake was 10.2 µg per day, which was lower than 15 µg as recommended in the Recommended Nutrient Intakes (RNI) for Malaysians (NCCFN, 2017). More than half of them (74.4%) did not achieve the RNI for vitamin D intake (Woon et al., 2019). In addition, Malay pregnant women were at a higher risk for vitamin D deficiency compared to the non-Malays due to religious and cultural reasons (Woon et al., 2019). The prevalence of vitamin D insufficiency and deficiency among pregnant women is at an alarming level, actions need to be taken to tackle this serious health problem as it is associated with adverse maternal and foetal outcomes. It is recommended that nutrition education emphasizing the consumption of vitamin D-fortified foods and sufficient sun exposure targeting the high-risk pregnant women is important to prevent low vitamin D in pregnant women.

5.3 Infant Feeding Practices in Infants during the First Year of Life

The present study found that 46.6% of the mothers complied with the WHO recommendations for infant feeding to exclusively breastfed the infants for at least 6 months and almost all mothers introduced complementary foods to the infants at 6 months of age (97.1%). The proportion of infants who were breastfed exclusively for the first 6 months in the present study is in accordance with the NHMS (IPH, 2016), whereby almost half of the infants under 6 months of age in Malaysia were exclusively breastfed (47.1%). Consistent findings were reported by Campbell et al. (2018) that 52.0% of the infants below 6 months of age in Bhutan were exclusively breastfed and 93.0% were given complementary foods between 6-8 months. The prevalence of exclusive breastfeeding in the present study is two times higher than the prevalence of exclusive breastfeeding for at least 6 months among children in Japan (22.7%) (Matsumoto et al., 2019) and China (13.8%) (Gao et al., 2019). The prevalence of introduction of complementary foods at six months in this study is in line with a study that reported a prevalence of 97.9% among Malaysian children below two years of age (Khor,

Tan, Tan, Chan, & Amarra, 2016) but was higher compared to 79.7% in China (Gao et al., 2019) and 50.1% in Australia (Koplin et al., 2010).

In terms of diet diversity, 89.4% of the infants in the present study did not meet the minimum dietary diversity at 6 months of age, while the proportion reduced to 45.5% at 12 months of age. The proportion of infants who complied with the minimum diet diversity in the present study was lower as compared to the NHMS that reported 66.4% of compliance in infants aged 6-23 months (IPH, 2016). Similar trends have been reported in the 2012 DHS Indonesia that 23.0% and 54.0% of infants received foods from at least four food groups at 6-8 months and 9-11 months, respectively (Blaney, Februhartanty, & Sukotjo, 2015).

Overall, the present study indicated that more than half of the mothers did not comply with WHO recommendations for exclusive breastfeeding at least 6 months. Major reasons that may influence mothers to stop exclusive breastfeeding include not having enough milk and returning to work after completing 3 months of maternity leave (Farahana, Norliza, & Nor Afiah, 2019; Tengku Alina, Wan Manan, & Mohd Isa, 2013). While almost all infants in the present study received timely complementary feedings, too few of them achieved the minimum dietary diversity at 6 months of age as recommended. At 6 months, infants were commonly fed with grain, roots, and tubers (69.5%), while consumption of flesh foods such as chicken and fish (18.0%), legumes, and nuts (2.2%) were low, and none of the infants was introduced to eggs. All infants were fed with grain, roots, and tubers at 12 months and the consumption of flesh foods increased to 79.2%. The consumption of legumes and nuts (5.3%) and eggs (10.5%) remained low at 12 months. Rice porridge or infant cereals are commonly introduced as the first complementary food in the Asia Pacific region (Inoue & Binns, 2014). Rice is the main staple food in Malaysia and can be easily prepared at home. Carrot, potato, fish, chicken meat, or anchovies are usually added in the rice porridge for infants. In addition, feeding a commercial infant cereal is common in Malaysia due to easy accessibility and convenience in preparation (Zulkjfli, Daw, & Abdul Rahman, 1996). Food groups including eggs, legumes and nuts, and flesh foods such as fish and seafood were less likely to be introduced to the infants at 6 months of age in the present study might be due to the avoidance of feeding infants with potential allergy-causing foods by the mothers. Up to 70.0% of the respondents in the present study were working mothers and they may face challenges in complying with the recommended minimum dietary diversity due to time constraints in preparing a variety of foods for the infants (Aria, Judhiastuty, Muchtaruddin, & Anuraj, 2019). Thus, there is a need for continued effort from the healthcare providers to promote and educate parents on optimum infant feeding practices in Malaysia. In addition, further investigation on the barriers of exclusive breastfeeding and low dietary diversity at 6 months of age are needed to address the low compliance to WHO recommendations in this study.

5.4 Prevalence of Allergic Diseases in Infants During the First Year of Life

In this prospective cohort study, the prevalence of ever had eczema during the first year of life was 27.6%, which is comparable with the Singapore GUSTO cohort study conducted in infants up to 18 months of age (23.6%) (Loo et al., 2015). Similar prevalence was also found in the Australia HealthNuts study which reported a cumulative prevalence of 28.0% parent-reported eczema in 12-month-old infants (Martin et al., 2013). In contrast, a low prevalence of parent-reported eczema (7.4%) has been reported among infants at 12 months of age in Thailand (Sangsupawanich et al., 2007). The differences can be explained by the used of different definitions of eczema across studies. Loo et al. (2015) defined eczema as parent report of a doctor diagnosis, Martin et al. (2013) based on parent report of a doctor diagnosis or used of a tropical steroid, and Sangsupawanich et al. (2007) based on parent report of eczema symptoms. In contrast, the present study defined eczema according to the UK Working Party's Diagnostic Criteria for Atopic Dermatitis (Williams et al., 1994).

While the prevalence of ever had parent-reported food allergy (20.8%) in infants during the first year of life was high, the IgE-mediated food allergy prevalence (3.8%) in the present study was comparable with the prevalence of parent-reported food allergy in Thai children below 3 years of age (6.4%) (Santadusit et al., 2005) and Singaporean infants aged 12 months (2.9%) (Tham et al., 2018). The large discrepancies between the prevalence of parent-reported food allergy in the present study compared with previous studies may be explained by the Dual Allergen Exposure Hypothesis which proposed that allergic sensitisation to foods may occur through exposure to low doses of food allergens through the skin due to food allergens in the environment being absorbed through a damaged skin barrier. This hypothesis is appealing in our study context because eczema is prevalent in our study populations, with up to 27.6% infants having parent-reported eczema during the first year of life. As reported in the Healthnuts Study, eczema frequently coassociates with food allergy, with 50% of those with early-onset moderately severe eczema developing food allergy by age 1 year (Martin et al., 2015).

Food sensitisation was found in 27.4% infants at 12 months of age in the present study, with the top five common food allergens being beef, peanut, egg white, soya, and egg yolk. Contradictory to the present study, the Singapore GUSTO cohort study reported a lower prevalence of food sensitisation (4.5%) in infants at 18 months of age using a skin prick test (Loo et al., 2016). The prevalence of food sensitisation reported in the present study was higher as compared to the food allergy prevalence because having the IgE antibodies towards a specific food allergen is not necessarily accompanied by clinical manifestations. Some individuals can consume the food that they are sensitised without showing any allergic reactions (Chokshi & Sicherer, 2016). Hence, repeat specific IgE blood testing should be performed to exclude false-positive results. The prevalence of sensitisation towards the common food allergens including peanut, eggs, soy, cow’s milk, shellfish, fish, and wheat in this study was much higher when compared to infants of the same age group from other birth cohorts (Kristinsdóttir et al., 2011; Osborne et al., 2011; Tham et al., 2018; Venter et al.,

2006). The different methods used to assess food sensitisation across studies such as allergen-specific IgE test, skin prick test, and oral food challenge could account for the inconsistent results.

The prevalence of food sensitisation based on allergen-specific IgE test in the present study indicates that infants with positive specific IgE tests towards food allergens may have a higher risk to develop food allergy symptoms in later life when the specific food was being consumed. Studies have shown that an allergen-specific IgE test is useful to determine whether a food challenge, the gold standard for food allergy diagnosis, should be performed due to its ability in predicting the food challenge outcome (Perry et al., 2004; Sindher et al., 2018). Previous studies also suggested that results from the allergen-specific IgE tests may identify the chance of true allergy for some of the common food allergens including egg, milk, peanut, soy, and wheat when high cut-off values were used (Sampson, 2001). In addition, elevated allergen-specific IgE levels in the first two years of life were associated with higher risk of allergic diseases later in life (Chiu et al., 2014). Hence, it is suggested that mothers need to be cautious when exposing infants to allergenic foods which may trigger food allergy based on the allergen-specific IgE test results and unnecessary diet restriction should be avoided.

Of particular concern, sensitisation to beef was found in 14.3% of the infants in the present study, which is comparable with Hon et al. (2010) who reported 18.0% beef sensitisation among children with eczema. Beef sensitisation is not uncommon although limited studies have been conducted in the paediatric population and most of the previous studies were conducted among the high-risk population (Fiocchi, Restani, & Riva, 2000; Hon et al., 2011). Bovine serum albumin (BSA) is a serum albumin protein derived from the cow that can trigger meat allergy (Fiocchi et al., 2000). BSA can also be found in other mammalian meats and milk which may result in cross-reactivity (Fiocchi et al., 2000; Hon et al., 2011; Theler, Brockow, & Ballmer-Weber, 2009). Studies have suggested that enzymatic digestion can affect the allergenicity of BSA and cooking also altered the reactivity to beef (Fiocchi et al., 1995; Fiocchi et al., 2000). In other words, infants who showed a positive test result for the beef allergen through skin prick test or sIgE test may not develop any clinical symptoms if they consumed cooked meat. Previous studies also suggested that beef sensitisation might be attributed to tick bites, where the galactose-α-1,3-galactose (α-gal) presents in the saliva of ticks may also found in red meat (Gonzalez-Quintela et al., 2014). However, the relationship between tick bites and beef sensitisation was not assessed in the present study. Although the result of sIgE test towards beef allergen was positive, beef elimination from the infant's diet is unnecessary as the infant may consume the cooked meat without showing clinical symptoms.

5.5 Prevalence of Malnutrition in Infants During the First Year of Life

Childhood malnutrition is an important public health problem in Malaysia, where the increasing prevalence of malnutrition in children under five years of age between the years 2015 and 2016 has been highlighted in the NHMS (IPH, 2016; UNICEF et al., 2019). The present study found a lower

prevalence of stunting (16.3%), wasting (7.6%), underweight (11.6%), and overweight (1.8%) in 12-month-old infants as compared to the prevalence of stunting (22.1%), wasting (11.2%), underweight (14.7%), and overweight (4.1%) in infants under 2 years of age in the NHMS (IPH, 2016). Findings from the present study indicate that the undernutrition problem was more prevalent than the overnutrition problem in infants during the first year of life. The first year of life is a period where infants experienced rapid growth and development, which involves tripling of birth weight and double the birth length (Lucas, Feucht, & Ogata, 2012). In the present study, the mean length of infants almost doubled from 49.2 cm at birth to 72.8 cm at 12 months of age, while the mean weight of infants almost tripled from 3.1 kg at birth to 8.6 kg at 12 months of age. Thus, growth monitoring in infants during the first year of life is important to identify problematic trends so that early intervention can be implemented to promote catch-up growth during this critical period before long-term growth is compromised (Lucas et al., 2012). Researches have suggested that impaired growth during the first 2 years of life in the forms of malnutrition such as stunting and obesity may lead to lower cognitive performance (Alam et al., 2020; Creese, Viner, Hope, & Christie, 2018) and higher risk of cardiovascular disease in adulthood (De Lucia Rolfe et al., 2018). The Malaysian government has implemented several strategies to address the malnutrition issues in children, such as the National Plan of Action for Nutrition of Malaysia (NPANM) (MOH, 2016a). Although preventive measures have been implemented, findings from the present study demonstrated that both undernutrition and overnutrition coexist during the first year of life and the progress is still far from the SDG target to end all forms of malnutrition by 2030 (UN, 2015). Apart from the existing strategies, continued efforts are required to identify other potential risk factors for early childhood malnutrition and should be targeted in future prevention strategies.

5.6 Associations Between Maternal Vitamin D Status During Late Pregnancy and Development of Allergic Diseases in Infants During the First Year of Life

The present study found that maternal vitamin D deficiency during late pregnancy was associated with an increased risk of ever had parent-reported food allergy in infants during the first year of life. Results from the present study were inconsistent with Weisse et al. (2013) that reported a positive association, while Hennessy et al. (2018) and Stelmach et al. (2015) reported no association between maternal vitamin D status during pregnancy and food allergy risk in infants. Although maternal vitamin D status during pregnancy was not measured by Koplin et al. (2016), they found that maternal use of vitamin D supplement during pregnancy was inversely associated with challenged-proven food allergy in infants. The plausible underlying mechanism for the association between maternal vitamin D status and infant's risk of food allergy remains unclear. It is likely that vitamin D in infants which is acquired from the mothers through the placenta can promote immune tolerance in infants by regulating the antigen-presenting cell function, triggers the induction of Treg cells, and modifies the Th cytokines response. Low levels of vitamin D may be inefficient at suppressing Th2 cells activation, which compromises immune tolerance to food antigens, and subsequently associated with an increased risk of food allergy (Finkel et al., 2015). In addition, low vitamin D

levels could lead to compromised intestinal barrier function, increase the susceptibility to gastrointestinal infections, and thus link to a higher risk of food allergy (Vassallo & Camargo, 2010).

In the present study, no associations between maternal vitamin D status during late pregnancy and ever had eczema in infants was found, which is in line with the findings reported by Loo et al. (2019) and Weisse et al. (2013). Studies examining the influences of maternal vitamin D status on eczema in infants have shown less consistent results, which can be explained by the U-shape associations, suggesting that both lower and higher levels of vitamin D are associated with a higher risk of eczema (Blomberg et al., 2017; Gale et al., 2018). While Gale et al. (2018) reported that maternal vitamin D levels of more than 75 nmol/L were associated with an increased risk of eczema, Blomberg et al. (2017) found that maternal vitamin D levels of less than 25 nmol/L increased the risk of eczema in infants. Results from several randomised controlled trials (RCT) showed that maternal vitamin D supplementation during pregnancy did not affect the risk of eczema in children at 3 years (Chawes et al., 2016; Goldring et al., 2013; Litonjua et al., 2016) and 6 years of age (Litonjua et al., 2020). Apart from methodological differences across studies, the null associations between maternal vitamin D status and eczema in the present study may be explained by genetic factors, which play a more important role in the development of childhood eczema. Evidence showed that mutations in the filaggrin gene have been strongly associated with the development of eczema (Palmer et al., 2006; Weidinger et al., 2008). Therefore, the potential for vitamin D to interact with genetic factors in explaining the development of childhood eczema should be considered in future studies

The present study found no significant associations between maternal vitamin D status during late pregnancy and food sensitisation in infants during the first year of life, which is consistent with the findings reported by Loo et al. (2019) among Singaporean children at 5 years of age. Similarly, findings from two RCTs showed that maternal vitamin D supplementation during pregnancy did not pose an effect on the development of food sensitisation in infants during the first 3 years of life (Chawes et al., 2016; Litonjua et al., 2016). In contrast, several birth cohorts have examined the association of maternal vitamin D status during pregnancy with the risk of food sensitisation in infants and demonstrated conflicting results (Chiu et al., 2015; Weisse et al., 2013). While Weisse et al. (2013) revealed that higher maternal vitamin D levels were associated with an increased risk of food sensitisation, Chiu et al. (2015) reported that a sufficient maternal vitamin D level during pregnancy is protective against food sensitisation in infants. It should be noted that the comparison of findings across studies might be difficult due to differences in terms of length of follow-up, the period of pregnancy at which maternal vitamin D levels were measured, methods of food sensitisation measurement such as skin prick test (Loo et al, 2019), or specific IgE-confirmed food sensitization (Chiu et al., 2015; Weisse et al., 2013). In the present study, no association was found between maternal vitamin D status and food sensitisation, and it is therefore speculated that other factors such as genetic factors may play a more important role in explaining this association. The Boston birth cohort conducted by Liu et al. (2011) showed that cord blood vitamin D levels were not associated with food sensitisation in early childhood; however, a significant inverse association

was found in children with particular genotypes. Therefore, further studies are needed to explore the interactions between genetic factors and vitamin D levels in explaining their relationships with food sensitisation.

In the present study, no associations were found between maternal vitamin D status and the development of eczema and parent-reported food allergy in infants over time. To the best of knowledge, no study has attempted to assess the link of maternal vitamin D status during pregnancy with early childhood eczema and food allergy with time interaction in prospective cohorts. In previous studies, eczema and food allergy in infants were measured separately at multiple time points and did not account for repeated occurrences of eczema or food allergy within the same child throughout the study period (Chiu et al., 2015; Gale et al., 2008; Loo et al., 2019; Weisse et al., 2013). In other words, the present study suggested that maternal vitamin D status during pregnancy significantly associated with the development of parent-reported food allergy throughout the first year of life, regardless of the time of assessment of the food allergy outcome.

5.7 Associations of Maternal Vitamin D Status During Late Pregnancy with Malnutrition and Growth Indicators in Infants During the First Year of Life

The present study found no associations between maternal vitamin D status during late pregnancy with all forms of malnutrition (stunting, wasting, underweight, and overweight) and growth indicators (WAZ, LAZ, WLZ, and BAZ) in infants during the first year of life. Similar findings were reported by Ong et al. (2016) that maternal vitamin D status during mid-pregnancy was not associated with WAZ. LAZ, and BAZ in Singaporean infants during the first 2 years of life. In contrast, Morales et al. (2015) and Toko et al. (2016) found that higher maternal vitamin D levels were associated with decreased odds of overweight or stunting in infants. Findings from previous RCTs demonstrated that prenatal vitamin D supplementation of 1000 IU (Brooke, Butters, & Wood, 1981) or 5000 IU (Roth, Perumal, Al Mahmud, & Baqui, 2013) during the third trimester of pregnancy was associated with increased weight, length, or LAZ in infants during the first year of life. The inconsistent results might be attributed to methodology differences across studies in terms of the time point at which maternal vitamin D status and malnutrition outcomes were measured, different classification of maternal vitamin D status, duration of follow-up, and confounders included in analysis. The exact mechanisms underlying the possible role of maternal vitamin D status on infant growth are unclear, but findings from previous studies proposed that the mechanism may be mediated through direct effects of vitamin D on calcium homeostasis and growth hormones such as insulin-like growth factor I (IGF-I) (Brunvand, Quigstad, Urdal, & Haug, 1996; Soliman et al., 2008). Therefore, further studies are needed to explore the interactions of vitamin D levels with calcium, parathyroid hormone, and IGF-I in explaining their relationships with childhood growth.

5.8 Associations Between Infant Feeding Practices and Development of Allergic Diseases in Infants During the First Year of Life

The present study found no significant associations between exclusive breastfeeding and the development of allergic diseases in infants during the first year of life. In other words, adherence to WHO recommendations on exclusive breastfeeding duration did not reduce the risk of allergic diseases in infants. Results of the present study supported the findings from three meta-analyses and several birth cohorts that reported no significant associations of breastfeeding with eczema and food allergy risk in infants and young children (Lin et al., 2019; Lodge et al., 2015; Yang et al., 2009). In contrast, some studies demonstrated that breastfeeding duration for 6 months and above were associated with an increased risk of eczema and food allergy in infants (Alkazemi et al., 2018; Matsumoto et al., 2019; Taylor-Robinson et al., 2016). Munblit and Verhasselt (2016) suggested that allergy is a modern disease that the beneficial effects of breast milk have not adapted to the needs of allergy prevention due to the rapid increase in allergy prevalence. Meanwhile, the protective effects of breastfeeding on allergic outcomes remain unclear due to individual variations in breast milk immunologically active molecules in relation to the country of origin, dietary pattern, and environmental exposures (Holmlund et al., 2010; Oddy & Rosales, 2010; Peroni et al., 2010). This is supported by previous studies demonstrated that mothers with a history of allergic diseases, living in an urban environment, and originate from an underdeveloped country had a significantly lower TGF-β1 and TGF-β2 concentrations in breast milk (Aihara et al., 2014; Laiho et al., 2003; Peroni et al., 2010; Rigotti et al., 2006). Thus, future studies should combine data on breastfeeding duration and pattern, as well as breast milk composition to understand the role of breastfeeding on allergic outcomes.

The present study found that there were no significant associations between introduction of complementary foods with the development of allergic diseases in infants during the first year of life. In other words, compliance with WHO recommendations for introduction of complementary foods to infants at 6 months of age has no protective effects on allergy risk. Results from the present study are in line with the findings reported in two birth cohorts, a case-control study, and a meta-analysis that no significant associations were found between age at introduction of complementary foods with eczema, food allergy, and food sensitisation in infants and young children (Alkazemi et al., 2018; Elbert et al., 2017; Tham et al., 2018; Waidyatillake et al., 2018). Contradictory to these findings, several birth cohorts showed that introduction of complementary foods below 6 months of age was associated with an increased risk of eczema, food allergy, and food sensitisation in infants and young children (Gao et al., 2019; Taylor-Robinson et al., 2016; Thorisdottir et al., 2019). Different study designs, methods for outcome assessment, and age categories for introduction of complementary foods may account for the discrepancies across studies. Meanwhile, while almost all infants in the present study met the WHO recommendations on complementary feeding (97.1%), the number for the infants who did not meet the recommendations are too few to detect a significant difference. To date, there is still no agreement on the ideal time for introducing complementary foods for allergy prevention. Different guidelines on the timing for complementary foods

introduction have been used across countries and professional bodies, which may lead to confusion among the clinicians and public. While WHO recommends complementary foods introduction at 6 months onwards (WHO, 2001), professional bodies such as the AAP, ASCIA, ESPGHAN, and MSAI suggest complementary foods to be introduced between 4-6 months (ASCIA, 2016; Fewtrell et al., 2017; Kleinman, 2000; MSAI, 2014). Emerging evidence suggests that introduction of allergenic foods such as peanut and eggs as early as 3 months can reduce the allergy risk (Du Toit et al., 2008; Du Toit et al., 2015; Perkin et al., 2016). In order to fully explain the relationships between introduction of complementary foods and allergy risk, future research should focus on the timing of allergenic food introduction.

The present study found that infants who met the minimum dietary diversity at 6 months were more likely to develop food sensitisation at 12 months of age, while no associations were found for eczema and food allergy. In other words, a more diverse diet was associated with an increased risk of food sensitisation in infants. In the present study, the associations between minimum dietary diversity at 6 months and allergic outcomes were assessed instead of 12 months because the infant's gut microbiota showed a large shift in the abundances of bacterial taxa started at 6 months when complementary foods were being introduced (Collado, Cernada, Baüerl, Vento, & Pérez-Martínez, 2012). Introduction of complementary foods starting from 6 months determine the stability of the gut microbiota and may determine the susceptibility to allergic diseases later in life (Laursen et al., 2016; Nwaru et al., 2014; Zhuang et al., 2019). Contradictory to the findings from the present study, previous studies reported that a less diverse diet was associated with higher risk of eczema, food allergy, and food sensitisation (Nwaru et al., 2014; Roduit et al., 2014). The possible explanation for the significant associations found in the present study might be due to gut colonisation and local immune networks are less established in infants and thereby early exposure to diverse food antigens at 6 months may increase the risk of food sensitisation at 12 months of age (Prescott et al., 2008). Studies on diet diversity and its relations with early childhood allergy have been limited and demonstrated inconsistent findings and thus warrant further study.

5.9 Associations of Infant Feeding Practices with Malnutrition and Growth Indicators in Infants During the First Year of Life

In the present study, while no associations were found between exclusive breastfeeding and all forms of malnutrition in infants, exclusive breastfeeding until 6 months was associated with decreased WAZ, LAZ, WLZ, and BAZ in infants at 12 months of age. In other words, compliance to WHO recommendations on exclusive breastfeeding are not protective against malnutrition but slower the growth rate in infants, which supported the results of two cohort studies (Budree et al., 2017; Woo et al., 2013). There are several possible explanations for exclusive breastfeeding on slower gain of weight and length in infants. First, differences in protein content and lipid profile of breast milk versus formula may contribute to different growth rate in infants (Bartok & Ventura, 2003). High protein content in formula may result in greater insulin response and could lead to the development

of adipose tissue and weight gain in infants (Lucas et al., 1980). In addition, the omega-6 and omega-3 ratio in formula may promote adipocyte growth and differentiation, as well as more inflammation in infant's body, which leads to weight gain or higher risk of obesity (Bartok & Ventura, 2003). Second, bioactive compounds in breast milk such as leptin, ghrelin, and IGF-I may help to regulate the growth of infants (Savino et al., 2005). Third, breastfed infants are capable to self-regulate their intake to meet nutritional needs. They are unlikely to be overfed by their mothers compared with formula-fed infants and, therefore reduce the risk of excessive weight gain (Griffiths, Smeeth, Hawkins, Cole, & Dezateux, 2009; McCrory & Layte, 2012).

The present study reported no significant associations between introduction of complementary foods and malnutrition in infants during the first year of life. Similar findings were found in two prospective cohort studies that timing of complementary foods introduction was not associated with any of the growth indicators; namely, LAZ, WAZ, WLZ, and BAZ in infants (Liu et al., 2019; Woo et al., 2013). In contrast, Moschonis et al. (2017) showed that introduction of complementary feeding to infants at 6 months onwards was associated with lower LAZ at 4-5 years of age, while Seach et al. (2010) have reported lower rates of overweight and obesity in children at 10 years of age who started complementary feeding later. For the case of diet diversity, no significant associations were found between minimum dietary diversity at 6 months and malnutrition in the present study, which is consistent with the findings reported in two cross-sectional studies conducted among infants below 2 years of age in Indonesia and Myanmar (Ahmad et al., 2018; Mya et al., 2019). In contrast, Udoh and Amodu (2016) reported that the risk of underweight and stunting were significantly higher among infants who did not meet the minimum dietary diversity between 6-12 months of age.

The non-significant associations of introduction of complementary foods and minimum dietary diversity with malnutrition found in the present study may be explained by the different reaction to complementary foods introduced at 6 months between breastfed and formula-fed infants (Huh, Rifas-Shiman, Taveras, Oken, & Gillman, 2011). Huh et al. (2011) reported that timing of complementary foods introduction was significantly associated with the risk of obesity in formula-fed infants, while no association was found among breastfed infants. Meanwhile, Bortolini and colleagues (2019) found that dietary diversity was significantly different between exclusively breastfed and formula-fed Brazilian infants. In addition, it is important to note that the endpoint of the present study was 12 months of age, which may have been too early to detect significant differences in growth rate, as significant findings from previous studies were detected among infants after the first year of life (Huh et al., 2011; Moschonis et al., 2017; Prado et al., 2019; Seach et al., 2010). Thus, future studies should distinguish between exclusively breastfed and formula-fed infants when examining the associations of complementary feeding and dietary diversity with malnutrition in infants and a longer follow-up period is recommended.

5.10 Associations Between Allergic Diseases and Malnutrition in Infants During the First Year of Life

The present study found that ever had parent-reported food allergy was associated with higher risk of wasting in infants during the first year of life. Similar results were reported by Beck et al. (2016) that infants who had food allergy were more likely to be shorter and lighter at age one year and continued to grow slowly at age 4 years. In contrast, Chong et al. (2018) and Flammarion et al. (2011) found that infants and young children with food allergy were more likely to be stunted, while no associations were found for wasting. The mechanisms underlying the associations between food allergy and malnutrition are not fully understood. The possible explanation for these significant associations may be due to mother of the food allergic children may avoid major food allergens when feeding their child (Mehta, Groetch, & Wang, 2013; Venter, Mazzocchi, Maslin, & Agostoni, 2017). Dietary restriction without proper medical advice or supervision may result in malnutrition (Low, Jamil, Md Nor, Kader Ibrahim, & Poh, 2019). Apart from food avoidance, Venter et al. (2017) suggested that impaired growth in children with food allergy might be related to a condition known as "sub-inflammation" whereby the absorption and utilisation of substrates were adversely affected. While studies assessing the links between allergic diseases and malnutrition in infants have been limited, further researches are needed to explore the underlying mechanisms of these associations.

5.11 Interrelationships between Maternal Vitamin D Status during Late Pregnancy, Parent-reported Food Allergy, and Wasting in Infants during the First Year of Life

In the present study, the interrelationships between maternal vitamin D status during late pregnancy, food allergy, and wasting in infants during the first year of life were assessed using a SEM. The SEM was developed based on results from the multivariable GLMM. The independent variable included in the SEM was maternal vitamin D status, while the dependent variables were ever had parent-reported food allergy and wasting. Confounding factors included in the SEM were based on results from the univariate analyses, where parity and maternal age were adjusted for parent-reported food allergy and birth weight was adjusted for wasting. Two additional confounding factors, namely, family history of allergic diseases and eczema were adjusted for parent-reported food allergy as previous evidence has identified their important role in predicting the risk of food allergy in infants (Koplin et al., 2013; Lack, 2008; Martin et al., 2015; Saunes, Øien, Storrø, & Johnsen, 2011).

The present study hypothesised that maternal vitamin D status during pregnancy was associated with the development allergic diseases and malnutrition in infants. The results of the SEM support the hypothesis, which demonstrates that deficient maternal vitamin D status during late pregnancy was associated with an increased risk for food allergy in infants during the first year of life. In addition, deficient maternal vitamin D status may increase the risk of wasting in infants, an effect that is mediated by food allergy development during the first year of life. The results of the present study

are similar to the findings from several birth cohorts which found that higher maternal vitamin D levels were protective against food sensitisation (Chiu et al., 2015) and promote growth in children (Eckhardt et al., 2015), and children with food allergy were more likely to be shorter and lighter (Beck et al., 2016). The present study extends this knowledge by showing the interrelationships between maternal vitamin D status, development of food allergy, and wasting in infants. Further confirmation of these findings is required.

The interrelationships between infant feeding practices, allergic diseases, and malnutrition were not tested in the SEM as no significant associations were found between these variables in the multivariable GLMM. This observation does not support the commonly held hypothesis that compliances with WHO recommendations on infant feeding may be protective against the development of allergic diseases and malnutrition in infants (Gao et al., 2019; Horta & Victoria, 2013; Udoh & Amodu, 2016; Roduit et al., 2014). The relationships between infants feeding practices, allergic diseases, and malnutrition remain to be elucidated and warrant further investigations

5.12 Strengths and Limitations of the Study

The major strengths of this study are in its design as a prospective cohort study, which allows for determining the causal relationships of maternal vitamin D status during late pregnancy and infant feeding practices with the development of allergic diseases and malnutrition in infants during the first year of life. In addition, information on the important potential confounding factors that were considered in the relationships between the exposure variables with the allergy and malnutrition outcomes were collected. To the best of knowledge, this is the first study that reported the role of food allergy as a mediator in the association between maternal vitamin D deficiency and wasting in infants.

Besides, maternal vitamin D status was objectively measured based on serum 25(OH)D concentrations in late pregnancy and categorised according to IOM classifications which allow for comparison with other studies. Blood test results on vitamin D status were given to the mothers upon request during the first postnatal follow-up at 3 months postpartum and simple suggestions on the consumption of foods containing vitamin D and sun exposure were given to those with vitamin D deficiency. As maternal vitamin D status was measured once at the third trimester of pregnancy and the respondents received the blood test result after delivery, this could avoid the potential bias on the exposure being measured.

Information on infant feeding practices were based on feeding on the previous day, which requires a short length of recall and was self-reported by the mothers, who are the primary caregivers of the infants. Thus, there was minimal potential for recall bias on the infant feeding data. In addition,

information on body weight and height of the infants were extracted from the medical records, which was measured by well-trained nurses using a standard protocol at the health clinics that may reduce the potential bias due to measurement error. Digital baby weighing scale in the health clinics was calibrated before used and was compared with a standard scale to ensure precise and consistent measurements between different health clinics.

Several limitations of the present study should be taken into consideration. First, the present study was conducted among mother-infant pairs from selected government health clinics in the state of Selangor and Federal Territory of Kuala Lumpur, Malaysia. Hence, the results may not be able to be generalised to the other populations. The government health clinics are the primary source providing regular antenatal care and were attended by pregnant women from multiracial groups and different socioeconomic status. A skewed population with the majority of the pregnant women were Malays was observed in the present study, which is in line with the report of the Malaysia national survey.

Second, maternal vitamin D status was measured once during the third trimester of pregnancy, thus unable to determine the changes of maternal vitamin D status over the course of pregnancy and their effects on the study outcomes. In addition, previous studies have demonstrated the important role of vitamin D status of the infants on the development of allergy and malnutrition. However, vitamin D status of the infants was not measured in the present study due to ethical considerations, safety concerns, budget constraints.

Parent-reported allergic diseases including eczema and food allergy may be subjected to recall and reporting bias. However, regular follow-up at multiple time points and the short time-lapsed between the follow-up may reduce the recall bias. Although symptoms of eczema in infants were self-reported by the mothers, the eczema status was categorised based on stringent criteria using the UK Working Party's Diagnostic Criteria, which may reduce the reporting bias.

Due to low numbers of infants who had IgE-mediated food allergy and overweight, there may be insufficient statistical power to detect the significant associations between the independent variables with these variables. In addition, the present study only assessed the development of eczema and food allergy in infants, while other atopic diseases including asthma and allergic rhinitis were not included because asthma and allergic rhinitis usually develop later in childhood around 4-8 years of age according to the allergic march, and are uncommon during the first year of life.

Attrition is a concern in prospective cohort studies which may lead to selection bias. However, there were no significant differences in majority of the characteristics between the respondents who completed the study and those loss to follow up, suggesting limited bias. Significant association was found between maternal vitamin D status and parent-reported food allergy in infants using the complete case analysis. However, these association was no longer significant when it was analysed

using the imputed data. Discrepancies between the results of complete case analysis and imputed dataset may be explained by the systematic differences between the observations included in and excluded from the analyses. In addition, standard errors may increase due to the uncertainty introduced by the multiple imputation.

Chapter 6

Conclusion and Recommendations

6.1 Conclusion

Vitamin D inadequacy were prevalent among third-trimester pregnant women in the present study. While adherence to the WHO recommendations on complementary feeding in infants was high, more than half of them did not comply with the exclusive breastfeeding recommendations. In addition, more than three-quarters of the infants did not meet the minimum dietary diversity at 6 months of age and almost half did not meet at 12 months of age. The present study found that about one-fourth of the infants developed eczema, one-fifth developed parent-reported food allergy, and about one-quarter had food sensitisation during the first year of life. The undernutrition problem, namely stunting, wasting, and underweight was more prevalent than the overnutrition problem among infants during the first year of life.

The present study suggested that maternal vitamin D deficiency during late pregnancy was associated with a higher risk of parent-reported food allergy in infants during the first year of life. In addition, infants who had parent-reported food allergy during the first year of life were more likely to be wasted. The associations between maternal vitamin D status during late pregnancy and wasting in infants during the first year of life may be mediated by parent-reported food allergy. No associations were found between infant feeding practices with the study outcomes.

6.2 Recommendations

As high prevalence of vitamin D insufficiency and deficiency were reported in the present study, future nutrition education should emphasise on the importance of vitamin D during pregnancy. High prevalence of non-compliances with WHO recommendations on infant feeding in the present study indicate that current nutrition programmes and activities on promoting and supporting appropriate infant feeding in accordance with the WHO recommendations seems to have had insufficient impacts. Thus, there is a need for better monitoring and nutritional counselling on infant feeding practices during postnatal care at the health clinics.

The high prevalence of allergic diseases among infants in the present study indicates that the allergic epidemic which was previously prevalent in the developed countries has now become common in the developing countries, such as Malaysia. The present study suggests that the double form of malnutrition which is a public health problem affecting all populations in Malaysia have their roots in early childhood, during the first year of life. Development of allergic diseases and poor nutrition status in early life may exert programming effects on long-term

health, growth, and development of the infants and thus, more studies identifying the risk factors for allergy and malnutrition development are warranted.

The present study suggests that nutrition education and counselling for pregnant women and lactating mothers at the health clinics and hospitals should emphasise on the importance of vitamin D, the risk of vitamin D deficiency during pregnancy and their related adverse outcomes, as well as the sources of vitamin D such as vitamin D fortified foods or supplements. In addition, information on the proper way to introduce new complementary foods to the infants should be emphasised in Malaysia Infant Feeding Guideline, for instance, introduce single-ingredient foods each time when feeding the baby for 3-5 days to observe for any food reactions. Mothers should be informed about the common food allergens as identified in the present study that may trigger a food allergic reaction. Management of food allergy should be done under the advice of the health professionals to avoid unnecessary food avoidance that may lead to faltering growth in the child. Further studies with a large sample size are required to confirm the findings from the present study and effects of maternal vitamin D status at different stages of pregnancy on the development of childhood allergy and malnutrition should be assessed.

The non-significant associations of infants feeding practices with allergic diseases and malnutrition in the present study suggested that other factors may play a more important role and warrant further investigation. As discussed earlier, maternal breast milk composition and feeding methods may play a more important role on allergy and malnutrition risk in infants. Therefore, future work should focus on assessing breastmilk composition and distinguish between breastfed and formula-fed infants to further explain these associations.

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Appendices

Appendix 1: Published Article on Research Protocol (Woon et al., 2018)

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BMC Pediatrics

STUDY PROTOCOL Open Access

Contribution of early nutrition on the development of malnutrition and allergic diseases in the first year of life: a study protocol for the Mother and Infant Cohort Study (MICOS)

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Abstract

Background: Nutrition and environmental factors are essential for the education of the neonatal immune system. Epidemiological evidence has shown that malnutrition and allergic diseases that occur during early childhood share similar protective and risk factors. This paper describes the protocol of the Mother and Infant Cohort Study (MICOS), which aims to determine the contribution of early nutrition to the development of malnutrition and allergic diseases in infants' first year of life.

Methods: MICOS is a prospective cohort study conducted at selected government health clinics in two states, namely Selangor and Wilayah Persekutuan Kuala Lumpur, Malaysia. Women in their third trimester of pregnancy are recruited into the study and their infants will be followed-up at 3, 6, and 12 months of age. Information on prenatal factors including socio-demographic characteristics, obstetric history, pre-pregnancy body mass index, gestational weight gain, smoking, family history of allergic diseases, maternal dietary intake and sunlight exposure during pregnancy are obtained through face-to-face interviews. Postnatal factors including dietary intake, sun exposure, and anthropometric measurements of the mothers, as well as feeding practices, dietary intake, anthropometric measurements, and development of allergic diseases of the infants are assessed at each follow-up. Blood samples are collected from the mothers in the third trimester to determine 25-hydroxyvitamin D levels as well as from the infants at age 12 months to determine atopic sensitisation.

Discussion: The concept of developmental origins of health and disease (DOHaD) which emphasises on the role of early life environments in shaping future health and disease susceptibility in adulthood has gained a huge interest in recent years. The DOHaD paradigm has influenced many fields of research including malnutrition and allergic diseases. While findings from the developed countries remain controversial, such studies are scarce in developing countries including Malaysia. The present study will determine the cause and effect relationship between early nutrition and the development of malnutrition and allergic diseases in infants' first year of life.

Keywords: MICOS, Infant, Early nutrition, Allergic diseases, Malnutrition

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Background

Inadequate intake of energy and nutrients may lead to malnutrition in the form of muscle wasting, stunted growth, and being underweight while excessive intake may lead to being overweight and obese [1]. Both forms of malnutrition occur among Malaysians. According to the National Health and Morbidity Survey (NHMS) 2015 Malaysia, approximately 17.7% of children below five years of age were stunted, 12.4% were underweight, 8.0% were wasted, and 7.6% were overweight [2]. Childhood malnutrition is linked to a high risk of mortality, lower levels of cognitive development, an increased susceptibility to childhood infectious diseases and lower levels of labor productivity in adulthood [3–7].

Allergy is an abnormal over-reaction or hypersensitivity reaction of the body caused by specific immunologic mechanisms which occur after an exposure to substances that are normally harmless to the human body [8]. Food allergy and eczema are the first manifestations of allergy, which usually appear during the first two years of life. Although many children outgrow their allergies, some still continue to have them. Additionally, some allergic disorders can change and progress to asthma and allergic rhinitis in later childhood. This phenomenon is known as the "atopic march" [9, 10]. The International Study of Asthma and Allergies in Childhood (ISAAC) reported that 12.6% of children (6–7 years old) in Malaysia have eczema, 5.8% have asthma, and 4.8% have allergic rhinitis [11]. Childhood allergies could lead to inappropriate diet elimination when parents are incorrectly advised and thus malnutrition, which will affect the quality of life of the patients as well as their families [12–14].

Malnutrition and allergic diseases are growing public health problems worldwide and are common diseases encountered during the first two years of life [10, 15]. As recent research demonstrated that nutrition is an essential prerequisite for the functionality of the immune system, both malnutrition and allergic diseases during childhood may have negative health consequences that persist into adulthood [10, 16]. Previous studies showed a significant association between allergic diseases and malnutrition [12, 17–22]. For example, food allergies can affect the growth and nutritional status of children with eczema. Therefore, there is a need to understand the role of early nutrition in preventing the first manifestation or progression of malnutrition and allergic diseases.

There is a growing body of evidence from research demonstrating that intrauterine exposures and early postnatal environment play a crucial role in determining the health and risk of disease later in life [23–25]. In addition, evidence from research revealed that early nutrition and lifestyle factors have long-lasting programming effects on the risk of later developing associated non-communicable diseases. Insults or stimuli that occur during the critical period, from pregnancy to early infancy, can trigger adaptations that lead to permanent changes in the structure and function of an organism, known as "programming" [26]. Early nutrition has been identified as one of the most important key players in programming; and thus, the right nutrition during the critical period is crucial to ensure proper growth and good health [25, 27].

The concept of early life nutrition refers to the maternal diet during pregnancy and lactation, as well as child feeding practices (breastfeeding and complementary feeding) [28]. Maternal nutrient requirements during pregnancy and lactation are increased in order to support fetal growth and production of breast milk [29]. During pregnancy, the supply of nutrients to the fetus is dependent on what mothers eat and the effectiveness of the placenta in transporting these nutrients to the fetus. A fetus may become undernourished when the nutrient supply does not meet its demand, thus resulting in fetal growth restriction, which is a major determinant of stunted linear growth and subsequent obesity in childhood [30]. On the other hand, maternal diet during lactation could influence her breast milk composition. Breastfeeding may protect infants against rapid weight gain and later obesity, which is possibly attributed to the bioactive components in breast milk that regulate an infant's appetite, metabolism, weight gain, and adiposity [31].

There are certain food items in a mother's diet during pregnancy and lactation such as fish and shellfish, peanut, and milk, which are potential food allergens, and could influence the risk of allergy among infants through in-utero allergen exposure transplacentally or transamniotically [32–34]. In-utero allergen exposure could influence the fetal immune response to shift towards development of tolerance or development of an allergic disease [34, 35]. Maternal dietary allergen exposure during lactation could influence the risk of allergy among infants through food allergens that are passed through human milk [36] which might promote tolerance in a newborn and subsequently reduce the risk of allergic diseases [18, 37]. Breast milk consists of an abundance of immunomodulatory components such as IgA, cytokines, chemokines, growth factors, and essential fatty acids which are essential to promote the development of the infant immune system [38–40]. A shorter duration of breastfeeding has been shown to be associated with an increased risk of asthma and allergic diseases in infants [41, 42]. Meanwhile, early introduction to allergenic food might decrease the risk of allergic diseases by promoting tolerance in infants [43, 44]. Apart from dietary allergen exposure, maternal intake of specific nutrients such as vitamin D and polyunsaturated fatty acids (PUFA) during pregnancy may also affect the risk of development of allergic diseases in offspring. Several studies from Western countries found that high maternal

vitamin D and total PUFA intake during pregnancy were associated with a decreased risk of allergic diseases in children [45–48].

Although there are many prospective cohort studies on the association between early life nutrition and childhood malnutrition or allergy, the majority of these works were conducted in developed countries and some of the outcomes remain controversial [17–20, 22, 46, 49]. In addition, these studies focused on a single outcome, even though both allergy and malnutrition share a similar risk factor, which is early life nutrition. The Mother and Infant Cohort Study (MICOS) is therefore designed to determine the association between early life nutrition and the development of malnutrition and allergy in infants. The prospective cohort study design of MICOS involves an assessment of pre- and postnatal dietary exposures at multiple time points. Additionally, the environmental factors, family history, and maternal obstetric history are assessed to provide a comprehensive assessment of factors related to the development of childhood malnutrition and allergy. The prevalence of allergic diseases and malnutrition will be assessed and the scientific evidence on the cause and effect relationship between early nutrition and the development of allergic diseases and malnutrition in infants will be investigated. The aim of this paper is to describe the rationale and methodology of MICOS in addressing the need to investigate the association of early nutrition with malnutrition and allergy.

Aim of the study

The present study aims to determine the contribution of early nutrition on the development of malnutrition and allergic diseases in infants at 12 months of age. The specific research questions to be answered by this study are as follows:

- What is the incidence of malnutrition in infants at 12 months of age?
- What is the incidence of allergic diseases in infants at 12 months of age?
- Is early nutrition associated with the development of malnutrition and allergic diseases in infants at 12 months of age?
- Is there any association between development of allergic diseases and malnutrition in infants at 12 months of age?

Methods/design

Study design and setting

MICOS is a prospective cohort study involving pregnant women in their third trimester of pregnancy (≥ 28 weeks of gestation) who are attending six randomly selected Maternal and Child Health clinics in the state of Selangor and the city of Kuala Lumpur, Malaysia. The Maternal and Child Health (MCH) clinics are the primary source providing antenatal and postnatal care to pregnant women. In the present study, pregnant women are enrolled at ≥28 weeks of gestation and are followed-up prospectively at 3, 6, and 12 months postpartum together with their infants (Fig. 1).

Recruitment of respondents

The respondents are selected using a cluster sampling method. A list of government health clinics in Selangor and Kuala Lumpur was obtained from the Selangor and Kuala Lumpur Health Departments. Six health clinics that met the inclusion criteria (government-funded and have a MCH clinic) were randomly selected. Pregnant women who are Malaysian, aged 18 years and above, gestational age ≥ 28 weeks, attending the selected government health clinics for antenatal check-up, and are planning to have postnatal check-up for at least one year at the same selected government health clinics are eligible to participate in this study. Women will be excluded if they are diagnosed with an immune deficiency, have a multiple pregnancy, have a preterm delivery before 37 weeks, or if their baby is born with congenital abnormalities. The objective of the study and the study procedure will be explained to the potential respondents at the clinic waiting area whilst they are waiting their turn for the antenatal check-up. Written informed consent for the respondents and their baby are obtained from the respondents who agree to participate in the study.

Sample size calculation

Sample size was calculated using the formula for cohort study [50] with 95% power and 5% significance level. A total of 371 pregnant women is required for the study. Taking into account for a design effect of 1.119 [51] and a possible attrition rate of 28.5% [52], the sample size is increased to 533 pregnant women.

Data collection

Recruitment of respondents began in November 2016 and is currently on-going. Respondents are followed over time and the details of the variables assessed at each assessment point in this study are shown in Table 1.

Instrumentations

Maternal questionnaires

At the first encounter, information is gathered from women who are in their third trimester of pregnancy by a face-to-face interview. The information gathered includes socio-demographic characteristics (including age, ethnicity, marital status, educational level, occupation, and monthly household income), obstetrical history, smoking during pregnancy, medication use, and family history of allergic diseases. Body weight and height of the pregnant women before and during pregnancy are extracted from

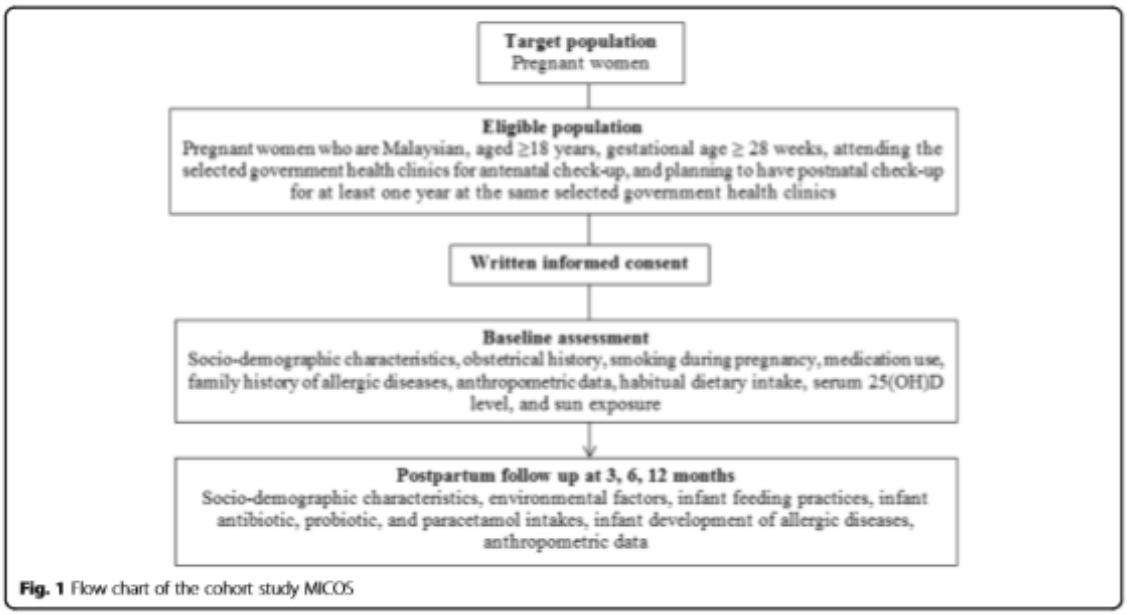

Fig. 1 Flow chart of the cohort study MICOS

their medical records, while body weight after delivery is measured at 3, 6, and 12 months. The measurements are recorded to the nearest 0.1 kg for weight and 0.1 cm for length, respectively. Pre-pregnancy Body Mass Index (BMI) is calculated by the weight in kilograms divided by the height in meters squared (kg/m2). Pre-pregnancy body weight status is classified into four categories based on the Institute of Medicine (IOM) Classification [53]. Total gestational weight gain (GWG) is calculated as the difference between the final recorded body weight at the last prenatal visit and the pre-pregnancy weight recorded at the first prenatal visit in the selected health clinics. The second and third trimesters mean weekly weight gain is estimated through the difference between the first and last weight recorded in the trimester divided by the number of weeks between the two observations. The maternal GWG is then categorised as inadequate, adequate, or excessive compared to the IOM [53] recommended weight gain based on their pre-pregnancy BMI group. Postpartum weight retention is calculated as the difference between the measured weight at 3, 6, and 12 months postpartum and pre-pregnancy weight, respectively.

Maternal habitual dietary intake

Maternal habitual dietary intake at the third trimester of pregnancy is assessed using a semi-quantitative food frequency questionnaire (FFQ), adapted from the Malaysian Adult Nutrition Survey (MANS) [54] and vitamin D FFQ [55]. Mothers are followed-up prospectively at 3, 6, and 12 months postpartum through face-to-face interviews. The serving size of the food consumed is estimated by using household measurements. The amount of food intake per day is calculated according to this formula: frequency of intake per day x serving size x total number of servings x weight of food in one serving [56]. Data obtained will then be entered into the Nutritionist Pro™ Diet Analysis software to obtain the energy and nutrient intake of the women.

Maternal vitamin D status

A peripheral venous blood sample (2 ml) is obtained from the women during their 3rd trimester of pregnancy by the nurses via venepuncture at the antecubital area to assess for vitamin D status. The ADVIA Centaur Vitamin D Total assay is used to determine maternal serum 25 hydroxy-vitamin D (25(OH)D) level. Maternal serum 25(OH)D level is then classified into vitamin D deficiency (< 30 nmol/L), vitamin D insufficiency (30–< 50 nmol/L) or vitamin D sufficient (≥50 nmol/L) [57].

Maternal sun exposure

Maternal exposure to direct sunlight during the third trimester of pregnancy is determined using a Seven-day Sun Exposure Record [58] and followed-up prospectively at 3, 6, and 12 months postpartum. Women are required to record the time they spent outdoors, type of clothing worn, sunscreen use, and the nature of outdoor activities during the previous week from 7 am to 7 pm. Body surface area (BSA) exposed is estimated by referring to the guidelines of clothing key [58]. Sun exposure index (SEI) is calculated by multiplying the amount of time spent outdoors with BSA exposed [58]. A higher SEI indicates a higher exposure to sunlight.

Table 1 Summary of data collection and timeline (Under section: Data collection - page 10)

Variables	Prenatal	Postnatal		
	3rd trimester	3 months	6 months	12 months
Mothers				
Age	√			
Ethnicity	√			
Educational level	√			
Occupation	√			
Monthly household income	√			
Obstetric history	√			
Pre-pregnancy body weight and height	√			
Body weight during pregnancy	√			
Body weight after delivery		√	√	√
Smoking during pregnancy	√			
Habitual dietary intake	√	√	√	√
Sun exposure	√	√	√	√
Serum 25(OH)D level	√			
Infants				
Sex		√		
Mode of delivery		√		
Body weight, length, head circumferences		√	√	√
Family history of allergic diseases	√			
Pet ownership		√	√	√
Day care attendance		√	√	√
Number of siblings		√		
Environmental tobacco smoke exposure		√	√	√
Infant feeding practices		√	√	√
Antibiotic, probiotic, and paracetamol intakes		√	√	√
Development of allergic diseases		√	√	√
Atopic sensitization				√

Infant questionnaires

Infant's sex and mode of delivery are extracted from their medical records during the follow up visit of the infants at 3 months. Environmental factors including pet ownership, daycare attendance, number of siblings, and environmental tobacco smoke exposure among the infants are obtained from their mothers through face-to-face interviews using The International Study of Asthma and Allergies in Childhood Questionnaires (ISAAC) Phase III Environmental Questionnaire [59] at 3, 6 and 12 months postpartum. Infant's weight, recumbent length, and head circumference data from birth to 12 months are extracted from their medical records. The anthropometric data at each age month is then converted to z-scores (length-for-age z-scores (LAZ), weight-for-age z-scores (WAZ), weight-for-length z-scores (WLZ), BMI-for-age z-scores (BMIZ), and head circumference z-scores (HCZ)) by using the WHO Reference 2007 SPSS macro package [60]. Infants nutritional status is defined as stunting (LAZ < -2SD), underweight (WAZ < -2SD), wasting (WLZ < -2SD), overweight (BMIZ > + 1SD), obese (BMIZ > + 2SD), and microcephaly (HCZ < -2SD) respectively, based on the WHO Child Growth Standards [60].

Infant feeding practices

Mothers are interviewed for infant feeding practices at 3, 6, and 12 months postpartum using the Infant and Young Child Feeding Questionnaire adapted from the Malaysian Third National Health and Morbidity Survey (NHMS III) [61] and are based on the indicators for infant and young child feeding (IYCF) suggested by WHO [62]. The seven core indicators include early initiation of breastfeeding, exclusive breastfeeding, continued breastfeeding, introduction of solid, semi-solid or soft foods, minimum dietary diversity, minimum meal frequency, and minimum acceptable diet, while the seven optional indicators include children never breastfed, continued breastfeeding, age-appropriate

breastfeeding, predominant breastfeeding, duration of breastfeeding, bottle feeding, and milk feeding frequency for non-breastfed children.

Infant antibiotic, probiotic, and paracetamol intakes

Antibiotic, probiotic, and paracetamol intake of the infants at 3, 6, and 12 months are assessed by asking the mother: "*Has your child ever consumed any antibiotic, probiotic, or paracetamol in the past three months?*" and "*If YES, how often in the past three months did your child consume it and how much did your child consume each time?*"

Infant development of allergic diseases

Eczema

Mothers are interviewed for the presence of eczema in infants at 3, 6, and 12 months based on five questions of the UK Working Party's Diagnostic Criteria for Atopic Dermatitis [63] with response options "yes" or "no". Eczema in infants is identified by the presence of an itchy skin condition plus two or more of the following; (i) history of involvement of skin creases such as folds of elbows, behind the knees, fronts of ankles, cheeks, or around the neck; (ii) a history of atopic disease in a first-degree relative; (iii) a history of a general dry skin; and (iv) visible flexural eczema.

Food allergy

Food allergy in infants at 3, 6, and 12 months are assessed by asking the mothers: "Has your child ever had a skin rash and sickness within two hours of eating some food?" and "Did these symptoms repeat each time the same food was consumed?" [64]. If positive answers are given to both of these questions, the mothers are required to select the type of food their children consumed that resulted in those symptoms. Options to select from include egg, peanut, tree nut, milk, shellfish, fish, wheat, and soy.

Asthma

The Asthma Predictive Index (API) [65] is used to determine the likelihood of infants who may develop asthma at 3, 6, and 12 months. A 'positive' API involves the presence of recurrent episodes of wheezing (more than three episodes per year) and one of two major criteria: (1) Asthma in a parent or (2) Eczema in infant; or two minor criteria: (1) Allergic rhinitis in infant and (2) Wheezing apart from colds in infant.

Rhinitis

Rhinitis in infants at 3, 6, and 12 months is assessed by the ISAAC questionnaire [66]. An infant is labelled to have rhinitis if the mothers report that the infant had a runny nose or sneezing episodes with no evidence of cold or flu.

Infant atopic sensitization

Peripheral venous blood samples are obtained from the infants via venepuncture at age 12 months. Approximately 1–2 mL of blood is collected by the medical assistants into 5-ml plain tubes. Serum samples are analyzed by using the OPTIGEN Allergen Specific Immunoglobulin E (IgE) Assay (Hitachi Chemical Diagnostics Inc., Japan) which enables the simultaneous determination of the infants' total IgE and specific IgE levels to a total of 35 food and inhalant allergens (egg yolk, egg white, soybean, peanut, milk, clam, crab, shrimp, cod fish, tuna, salmon, rice, wheat, banana, orange, sesame seed, chocolate, chicken, beef, mucor, timothy grass, bermuda glass, *Alternaria*, *Aspergillus*, *Candida*, *Cladosporium*, *Penicillium*, dog dander, cat dander, cockroach mix, housedust, *Mite Farinae*, *Mie Pteronyssinus*, *Blomis Tropicalis*, and latex). The results obtained from the test in net luminescence units (LU), are classified into class 0 (0–26 LU), class 1 (27–65 IU), class 2 (66–142 LU), class 3 (143–242 LU) and class 4 (> 243 LU) using the Chemiluminescent Assay (CLA) Class Allergy Scoring System (Hitachi Chemical Diagnostics Inc., Japan). Class ≥1 is interpreted as positive, indicating that the infants are sensitised to a specific food or aero-allergens.

Data analysis

The IBM SPSS Statistics 24 software (SPSS Inc., Chicago, IL, USA) will be used to analyse the data. Descriptive statistics and univariate analysis will be performed to describe the data. Hierarchical linear regression analysis with confounders are forcibly entered to examine the association between various exposure variables and the longitudinal outcomes. Data will be presented as relative risk (RR) with 95% confidence interval. Kaplan-Meier test and Cox regression analysis will be performed to analyse the time-to-event data and hazard ratios (HR) with a 95% confidence interval will be reported.

Discussion

About 60% of allergies appear during the first year of life [10]. The "hygiene hypothesis" originally proposed by Strachan [67] suggests that environmental influences such as decreased or absence of microbial exposures in early life have an adverse effect on the development of the immune system, which may lead to the development of allergic diseases. The concept of early environmental influences on later disease also draws on the increasing interest in fetal programming, known as the "Barker's hypothesis" [23]. Barker suggested that nutritional conditions during fetal life can influence the metabolism and occurrence of disease during adult life. Fetal undernutrition in middle to late gestation can affect fetal growth, which may contribute to an increased risk of non-communicable diseases such as coronary heart disease in later life. Barker's hypothesis was then further extended to the developmental origins of health and disease (DOHaD)

which emphasises the role of both the pre- and postnatal nutritional environment in determining adult diseases [24]. These three hypotheses suggests that early life nutritional environment can have lifetime consequences on later health. Hence, understanding the contribution of early nutrition, from pregnancy to early infancy is important to prevent the first manifestation of allergy or its progression, as well as early childhood malnutrition, which in turn lowers the risk of diseases in later life.

The prospective cohort study design of MICOS will generate a better understanding on the cause-effect relationship between early life nutrition and development of childhood malnutrition and allergy. In Malaysia, studies that examined the concept of early nutritional programming using a cohort study design are scarce. The USM Pregnancy Cohort Study was the first cohort study conducted in the state of Kelantan, Malaysia that linked maternal dietary exposures during pregnancy with birth outcomes in infants [68]. Another cohort study is being conducted in the state of Negeri Sembilan, Malaysia to determine early nutrition, growth and cognitive development of infants from birth to 2 years of age and is currently on-going [69]. Hence, the results of this study will fill the knowledge gap in this region by providing evidence for the role of early nutrition on growth and allergy development. In addition, the IgE blood test used in MICOS will help in identifying the prevalence of allergen sensitisation among infants in Malaysia. The incidence of allergic diseases and malnutrition that will be reported in the present study can enlighten the health professionals, policy makers as well as the public on the importance of early diagnosis of allergic diseases and malnutrition among infants. Through this study, we expect to contribute new knowledge and evidence of the association between early nutrition, childhood malnutrition and allergy which may be useful in helping health professionals and policy makers to develop dietary practice guidelines for pregnant women and infants to optimise the early life environment to ensure the health of future generations.

Abbreviations

25(OH)D: 25 hydroxy vitamin D; BMI: Body mass index; BSA: Body surface area; CLA: Chemiluminescent assay; FFQ: Food frequency questionnaire; GWG: Gestational weight gain; IgE: Immunoglobulin E; IOM: Institute of Medicine; ISAAC: International Study of Asthma and Allergies in Childhood; IYCF: Indicators for infant and young child feeding; JKEUPM: Ethics Committee for Research Involving Human Subjects, Universiti Putra Malaysia; LU: Net luminescence units; MANS: Malaysian Adult Nutrition Survey; MICOS: Mother and Infant Cohort Study; MREC: Medical Research and Ethics Committee; NHMS: National Health and Morbidity Survey; RNI: Recommended Nutrient Intakes for Malaysians; SEI: Sun exposure index; UK: United Kingdom; WHO: World Health Organization

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Authors' contributions

YSC led the project, contributed to the design of the study, supervising the study, provided critical input, and drafting and finalizing the manuscript. FCW made contributions to the design and conduct of the study, drafting and finalizing the manuscript. IHI, YMC, GA, WYG, and AHAL were involved in the study design and provided critical input on the initial draft of the manuscript. MB will be involved in the analysis and interpretation of data. All authors reviewed and approved the manuscript for publication.

Ethics approval and consent to participate

The study was approved by the Ethics Committee for Research Involving Human Subjects, Universiti Putra Malaysia (JKEUPM) [Reference number: FPSK (FR16)P006] and the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia [Reference number: NMRR-16-1047-30,685]. Permission to conduct the study at the selected government health clinics was obtained from the State Health Department, District Health Office, medical officer of the selected government health clinics, and matron of the Maternal and Child Health Unit of the selected health clinics. Written informed consent for the respondents and their baby are obtained from the respondents prior to data collection.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflicts of interest.

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Appendices

Appendix 2: Approval Letter - Ethics Committee for Research Involving Human Subjects, Universiti Putra Malaysia (JKEUPM)

UNIVERSITI PUTRA MALAYSIA
BERILMU BERBAKTI

PEJABAT TIMBALAN NAIB CANSELOR (PENYELIDIKAN DAN INOVASI)
OFFICE OF THE DEPUTY VICE CHANCELLOR (RESEARCH AND INNOVATION)

Reff. : UPM/TNCPI/RMC/1.4.18.2 (JKEUPM)
Date : 9st June 2016

Dr Chin Yit Siew
Department of Nutrition and Dietetics
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
Serdang, Selangor

Dear Madam,

RESEARCH PROJECT: CONTRIBUTION OF MATERNAL DIETARY INTAKE DURING PREGNANCY AND LACTATION AND FEEDING PRACTICES ON DEVELOPMENT OF ALLERGIC DISEASES AND MALNUTRITION IN INFANTS AT 12 MONTHS OF AGE AT SELECTED HEALTH CLINICS IN SELANGOR AND KUALA LUMPUR
PROJECT REF. NO: FPSK (FR16) P006

RESEARCHER : WOON FUI CHEE
SUPERVISOR : DR CHIN YIT SIEW

The Ethics Committee for Research involving Human Subjects of University Putra Malaysia (JKEUPM) has studied the proposal for the above project and found that there were no objectionable ethical issues involved in the proposed study.

Please find the list of documents received and reviewed with reference to the study and committee members who reviewed the documents (as attached).

Notwithstanding above, we will not be responsible for any misconduct on the part of researcher in the course of carrying out the research.

Thank you.

"WITH KNOWLEDGE WE SERVE"

Sincerely yours,

PROF. DATO' DR. ABDUL JALIL NORDIN
Chairperson
Ethics Committee for Research involving Human Subjects (JKEUPM)
Universiti Putra Malaysia

Pejabat Timbalan Naib Canselor (Penyelidikan dan Inovasi), Universiti Putra Malaysia, 43400 UPM Serdang, Selangor Darul Ehsan, Malaysia
Pejabat Timbalan Naib Canselor (P&I) 603-8947 1293 603-8945 1646, Pejabat Pentadbiran TNCPI 603-8947 1608 603-8945 1673,
Pejabat Pengarah, Pusat Pengurusan Penyelidikan (RMC) 603-8947 1601 603-8945 1596, Pejabat Pengarah, Putra Science Park (PSP)
603-8947 1291 603-8946 4121 http://www.tncpi.upm.edu.my

ETHICS COMMITTEE FOR RESEARCH INVOLVING HUMAN SUBJECTS
(JKEUPM)
UNIVERSITI PUTRA MALAYSIA

Research title	:	**Contribution of Maternal Dietary Intake During Pregnancy and Lactation and Feeding Practices on Development of Allergic Diseases and Malnutrition in Infants at 12 Months of Age at Selected Health Clinics in Selangor And Kuala Lumpur**
Study Site	:	**Selangor And Kuala Lumpur**
JKEUPM Ref No.	:	**FPSK(FR16)P006**
Researcher	:	**Woon Fui Chee**
Supervisor	:	**Dr Chin Yit Siew**

Documents received and reviewed with reference to the above study:

1. Ethics Application Form, Version 1 dated 29/4/2016
2. Respondent Information Sheet & Consent (English), Version 1 dated 29/4/2016
3. Proposal (English), Version 2 dated 27/5/2016
4. Questionnaire (English), Version 1 dated 29/4/2016.
5. Curriculum Vitae of:
    a. Dr Chin Yit Siew
    b. Dr Mohd Nasir Mohd Taib
    c. Assoc Prof Dr Intan Hakimah Ismail
    d. Dr Chan Yoke Mun
    e. Dr Amir Hamzah Abdul Latif
    f. Dr Geeta Appanah
    g. Dr Gan Wan Ying

The University Research Ethics Committee, Universiti Putra Malaysia (JKEUPM) operates in accordance to the ICH-GCP Guidelines.

Decision by JKEUPM:

[X] Approved

[X] **Permission MUST BE OBTAINED from the respective hospitals/ institutions before conducting the research**

[ ] Disapproved

Please note that the approval is valid until 9st June 2017.

Researchers should comply with the following:

I. Complete a Study Final Report upon study completion (Form D).

II. Ethical approval is required in the case of amendments/ changes to the study documents/ study sites/ study team.

III. Applicable for Clinical Trial Studies and Clinical interventional Studies only: Progress Report has to be submitted to JKEUPM at every 6 months from the date of approval (Form C). Report occurrences of all Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reaction (SUSARs) and Protocol Deviation/ Violation at all JKEUPM approved sites to JKEUPM. SAEs are to be reported within 15 calendar days from awareness of event by investigator. Initial report of SUSARs are to be reported as soon as possible but not later than 7 calendar days from awareness of event by investigator, followed by a complete report within 8 additional calendar days.

The required forms can be obtained from the Ethics Committee for Research Involving Human Subjects (JKEUPM) website (http://www.rmc.upm.edu.my/muatturun).

Date of Approval: 9st June 2016

Members of the JKEUPM who reviewed the documents:

i. Primary Reviewer: Prof Dr Sherina Mohd Sidik, Assoc Prof Dr Hejar
ii. Lay Person: Dr Rojanah Kahar

.....

PROFESSOR DR. ABDUL JALIL NORDIN
Chairperson,
Ethics Committee for Research involving
Human Subjects (JKEUPM),
Universiti Putra Malaysia

Appendices

Appendix 3: Approval Letter - Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia)

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(Medical Research & Ethics Committee)
KEMENTERIAN KESIHATAN MALAYSIA
d/a Institut Pengurusan Kesihatan
Jalan Rumah Sakit, Bangsar
59000 KUALA LUMPUR

Tel.: 03-2287 4032/2282 0491/2282 9085
03-2282 9082/2282 1402/2282 1449
Faks: 03-2282 0015

Ruj. Kami : (12)KKM/NIHSEC/P16-962
Tarikh : 3 Ogos 2016

DR CHIN YIT SIEW
WOON FUI CHEE
UNIVERSITY PUTRA MALAYSIA (UPM)

Tuan/ Puan,

NMRR-16-1047-30685 (IIR)
Contribution of maternal dietary intake during pregnancy and lactation and feeding practices on development of allergic diseases and malnutrition in infants at 12 months of age at selected health clinics in Selangor and Kuala Lumpur.

Dengan hormatnya perkara di atas adalah dirujuk.

2. Bersama dengan surat ini dilampirkan surat kelulusan saintifik dan etika bagi projek ini. Segala rekod dan data subjek adalah SULIT dan hanya digunakan untuk tujuan kajian dan semua isu serta prosedur mengenai ***data confidentiality*** mesti dipatuhi.

3. Penyelidik bersama yang terlibat di dalam kajian ini ialah:
- Dr Amir Hamzah bin Dato' Abdul Latiff
- Dr Chan Yoke Mun
- Dr Gan Wan Ying
- Dr Geeta Appannah
- Prof Madya Dr Intan Hakimah Ismail
- Dr Mohd. Nasir bin Mohd. Taib

4. Kebenaran daripada Pegawai Kesihatan Daerah/Pengarah Hospital dan Ketua-Ketua Jabatan atau pegawai yang bertanggung jawab disetiap lokasi kajian di mana kajian akan dijalankan mesti diperolehi sebelum kajian dijalankan. Tuan/Puan perlu akur dan mematuhi keputusan tersebut. Sila rujuk kepada garispanduan Institut Kesihatan Negara mengenai penyelidikan di Institusi dan fasiliti Kementerian Kesihatan Malaysia (Pindaan 01/2015) serta lampiran *Appendix 5* untuk templet surat memohon kebenaran tersebut.

5. Adalah dimaklumkan bahawa kelulusan ini adalah sah sehingga **2 Ogos 2017**. Dato'/Dr./ Tuan/ Puan perlu menghantar perkara-perkara berikut kepada JEPP mengikut kesesuaian.Borang-borang berkaitan boleh dimuatturun daripada laman web JawatakuasaEtika&Penyelidikan Perubatan (JEPP) (http://www.nih.gov.my/mrec).

i. Borang ***Continuing Review Form*** perlu dihantar ke JEPP selewat-lewatnya satu (1) bulan sebelum tamat tempoh kelulusan ini bagi memperbaharui kelulusan etika.
ii. ***Study Final Report*** perlu dihantar ke JEPP pada penghujung kajian.
iii. Mendapat kelulusan etika sekiranya terdapat pindaan ke atas sebarang dokumen kajian/ lokasi kajian/ penyelidik.
iv. Kajian berkenaan intervensi klinikal sahaja: Laporan mengenai ***all Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reaction (SUSARs)*** dan ***Protocol Deviation / Violation*** di lokasi kajian yang Diluluskan oleh JEPP jika berkenaan. *SAE* perlu dilaporkan dalam tempoh 15 hari calendar dari kesedaran kejadian (*awareness of event)* oleh penyelidik. Laporan awal *SUSAR* perlu dikemukakan seawal mungkin tapi tidak melewati 7 hari kalendar dari kesedaran kejadian oleh penyelidik, disusuli dengan laporan lengkap dalam tempoh tambahan lapan (8) hari kalendar.

6. Bilangan subjek /pesakit/ responden yang disasarkan untuk menyertai kajian ini di Malaysia adalah **918.**

7. Sila ambil maklum bahawa sebarang urusan surat-menyurat berkaitan dengan penyelidikan ini haruslah dinyatakan nombor rujukan surat ini untuk melicinkan urusan yang berkaitan.

Sekian terima kasih.

BERKHIDMAT UNTUK NEGARA

Saya yang menurut perintah,

.....
DATO' DR. CHANG KIAN MENG
Pengerusi
Jawatankuasa Etika & Penyelidikan Perubatan
Kementerian Kesihatan Malaysia

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(Medical Research & Ethics Committee)
KEMENTERIAN KESIHATAN MALAYSIA
d/a Institut Pengurusan Kesihatan
Jalan Rumah Sakit, Bangsar
59000 KUALA LUMPUR

Tel.: 03-2287 4032/2282 0491/2282 9085
03-2282 9082/2282 1402/2282 1449
Faks: 03-2282 0015

Ruj. Kami : (13)KKM/NIHSEC/P16-962
Tarikh : 3 Ogos 2016

NMRR-16-1047-30685 (IIR)
Contribution of maternal dietary intake during pregnancy and lactation and feeding practices on development of allergic diseases and malnutrition in infants at 12 months of age at selected health clinics in Selangor and Kuala Lumpur.

PRINCIPLE INVESTIGATOR:
DR CHIN YIT SIEW
WOON FUI CHEE
UNIVERSITY PUTRA MALAYSIA (UPM)

Documents received and reviewed with reference to the above study:

1. Study Protocol version 2 , dated 29-07-2016
2. Patient information sheet (English) & Informed Consent Form (English) version 2, dated 29-07-2016
3. Patient information sheet (BM) & Informed Consent Form (BM) - version 2, dated 29-07-2016
4. Questionnaire version 1, dated 21-06-2016
5. Follow-up Review Report version 1, dated 29-07-2016
6. CV and IA-HOD-IA of:
   Dr Chin Yit Siew
   Woon Fui Chee
   Dr Amir Hamzah Bin Dato' Abdul Latiff
   Dr Chan Yoke Mun
   Dr Gan Wan Ying
   Dr Geeta Appannah
   Prof Madya Dr Intan Hakimah Ismail
   Dr Mohd. Nasir Bin Mohd. Taib

Please note that the approval is valid until **2 August 2017**. The following items are to be submitted tothe Medical Research and Ethics Committee (MREC) as appropriate.The required forms can be obtained from the MREC website (**http://www.nih.gov.my/mrec**).

I. The **Continuing Review Form** is to be submitted to MREC at least one (1) months before the expiry of the approval.

II. The **Study Final Report** is to be submitted to MRECupon study completion.
III. Ethical approval is required in the case of **amendments / changes** to the **study documents/ study sites / study team**.
IV. **Applicable for Clinical interventional Studies only:** Report occurrences of **all Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reaction (SUSARs)** and **Protocol Deviation / Violation** at all MREC approved sites to MREC. SAEs are to be reported within 15 calendar days from awareness of event by investigator. Initial report of SUSARs are to be reported as soon as possible but not later than 7 calendar days from awareness of event by investigator, followed by a complete report within 8 additional calendar days.

2. The number of subjects/ patients / respondents targeted to enroll in this study in Malaysia is **918**.

3. Please take note that the reference number for this letter must be stated in all correspondence related to this study to facilitate the process.

Comments (if any):

Project Sites:

KLINIK KESIHATAN AMPANG
KLINIK KESIHATAN BANDAR SRI PUTRA
KLINIK KESIHATAN BANGI
KLINIK KESIHATAN BATU 14
KLINIK KESIHATAN BATU 9 CHERAS
KLINIK KESIHATAN BERANANG
KLINIK KESIHATAN IBU DAN ANAK BANDAR TUN RAZAK
KLINIK KESIHATAN IBU DAN ANAK CHERAS
KLINIK KESIHATAN IBU DAN ANAK DESA PANDAN
KLINIK KESIHATAN IBU DAN ANAK JALAN RAJA ABDULLAH
KLINIK KESIHATAN IBU DAN ANAK KAMPUNG PANDAN
KLINIK KESIHATAN IBU DAN ANAK METRO PRIM
KLINIK KESIHATAN IBU DAN ANAK SALAK SELATAN
KLINIK KESIHATAN IBU DAN ANAK SEGAMBUT
KLINIK KESIHATAN IBU DAN ANAK TAMAN PANTAI INDAH
KLINIK KESIHATAN IBU DAN ANAK TAMAN SRI SENTOSA
KLINIK KESIHATAN IBU DAN ANAK TAMAN TUN DR ISMAIL
KLINIK KESIHATAN KAJANG
KLINIK KESIHATAN KELANA JAYA
KLINIK KESIHATAN PAYA JARAS
KLINIK KESIHATAN PUCHONG
KLINIK KESIHATAN SEKSYEN 19
KLINIK KESIHATAN SEMENYIH
KLINIK KESIHATAN SERI KEMBANGAN
KLINIK KESIHATAN SHAH ALAM SEKSYEN 7
KLINIK KESIHATAN SUNGAI CHUA
KLINIK KESIHATAN TAMAN MEDAN

Decision by Medical Research & Ethics Committee:
(√) Approved
( ) Disapproved

Date of Approval: 3rd August 2016

DATO' DR. CHANG KIAN MENG
Chairperson
Medical Research & Ethics Committee
Ministry of Health Malaysia

Appendices

Appendix 4: Approval Letter - Selangor State Health Department

JABATAN KESIHATAN NEGERI SELANGOR
Tingkat 9, 10, 11 & 17, No. 1, Wisma Sunway,
Jalan Tengku Ampuan Zabedah C 9/C,
Seksyen 9, 40100 Shah Alam,
Selangor Darul Ehsan.

Tel : 03-51237333, 51237334, 51237335
Faks : 03-51237202 (Pengarah), 51237209 (Pengurusan), 03-51237299 (Perubatan), 51237389 (Pergigian), 51237399 (Kesihatan Awam), 03-55108977 (Farmasi), 55185195 (Keselamatan Dan Kualiti Makanan)
Portal Rasmi : www.jknselangor.moh.gov.my

Ruj Kami : JKNS/KA/Q-712/04-01 Jld 3 (11)
Tarikh : 23 September 2016

Dr Chin Yit Siew
Ketua Penyelidik/Ketua Pusat Penyelidikan Kecemerlangan
Pemakanan dan Penyakit Tidak Berjangkit
Fakulti Perubatan dan Sains Kesihatan
Universiti Putra Malaysia
43400 UPM Serdang
Selangor Darul Ehsan

Tuan/Puan,

MAKLUMBALAS PERMOHONAN KEBENARAN MENJALANKAN PENYELIDIKAN DI KLINIK KESIHATAN DI BAWAH JABATAN KESIHATAN NEGERI SELANGOR

Dengan hormatnya saya merujuk kepada perkara di atas dan surat yang bertarikh 16 Ogos 2016 adalah berkaitan .

2. Sukacita dimaklumkan bahawa Bahagian Kesihatan Awam, Jabatan Kesihatan Negeri Selangor **tiada halangan** untuk membenarkan pihak tuan/puan untuk menjalankan kajian yang bertajuk "*Contribution of maternal dietary intake during pregnancy and lactation and feeding practices on development of allergic diseases and malnutrition in infants at 12 months of age at selected health clinics in Selangor and Kuala Lumpur*" di klinik-klinik kesihatan di daerah Petaling dan Hulu Langat di Selangor sekiranya pihak tuan/puan memenuhi perkara-perkara berikut :

i. Semua permohonan kajian mesti didaftarkan secara online di National Medical Research Registrer (www.nmrr.gov.my)

ii. Kajian yang mempunyai aspek etika mesti memperolehi kelulusan dari Jawatankuasa Etika dan Penyelidikan Perubatan (JEPP), KKM

-Sila serahkan se salinan surat kelulusan Jawatankuasa Etika dan Penyelidikan Perubatan ,(JEPP) Kementerian Kesihatan Malaysia kepada Ketua Unit Kualiti (Kesihatan Awam), Jabatan Kesihatan Negeri Selangor setelah memperolehinya

iii. Melantik pegawai dari Jabatan Kesihatan Negeri atau Pejabat Kesihatan Daerah di mana data diperolehi, sebagai pegawai penyelidik bersama (jika perlu).

iv. Membentangkan hasil kajian kepada pihak kami setelah kajian selesai.

v. Memberikan se salinan hasil kajian kepada pihak kami untuk bahan bacaan dan rujukan pegawai-pegawai di jabatan ini.

vi. Sebarang penerbitan, diseminasi atau sebarang hasil penyelidikan tersebut sama ada melalui penulisan, pengiklanan, pembentangan atau untuk ke media perlu mendapat kelulusan Ketua Pengarah Kesihatan Malaysia terlebih dahulu.

4. Oleh yang demikian, diharapkan agar pihak tuan/puan dapat berbincang terlebih dahulu dengan Pegawai - Pegawai Kesihatan Daerah yang terlibat sebelum memulakan kajian tersebut.

Kerjasama dan perhatian tuan/puan adalah dihargai dan didahului dengan ucapan terima kasih.

Sekian.

"BERKHIDMAT UNTUK NEGARA"

"PENYAYANG, KERJA BERPASUKAN DAN PROFESIONALISMA ADALAH BUDAYA KERJA KITA"

Saya yang menurut perintah,

(DR. LING HE MEY, NO MPM 26748)
Timbalan Pengarah Kesihatan Negeri (Kesihatan Awam)
b.p. Pengarah Kesihatan Negeri,
Jabatan Kesihatan Negeri Selangor

MAKLUMBALAS PERMOHONAN KEBENARAN MENJALANKAN PENYELIDIKAN DI KLINIK KESIHATAN DI BAWAH JABATAN KESIHATAN NEGERI SELANGOR

s.k:-

Pengarah Kesihatan Negeri,
Jabatan Kesihatan Negeri Selangor

Pegawai Kesihatan Daerah
Pejabat Kesihatan Daerah Petaling

Pegawai Kesihatan Daerah
Pejabat Kesihatan Daerah Hulu Langat

Appendices

Appendix 5: Approval Letter - Kuala Lumpur and Putrajaya Health Department

JABATAN KESIHATAN WILAYAH PERSEKUTUAN
KUALA LUMPUR DAN PUTRAJAYA
Jalan Cenderasari,
50590 Kuala Lumpur.

Ruj. Kami : Bil.(17)dlm.JKWPKL/204/1bhg.5
Tarikh : 26 Ogos 2016

Dr. Chin Yit Siiew
Ketua Penyelidik / Ketua
Pusat Penyelidikan Kecemerlangan
Pemakanan dan Penyakit Tidak Berjangkit
Fakulti Perubatan dan Sains Kesihatan
Universiti Putra Malaysia
43400 UPM Serdang
Selangor Darul Ehsan

Puan,

PERMOHONAN KEBENARAN UNTUK MENJALANKAN PENYELIDIKAN DI KLINIK KESIHATAN DI BAWAH JABATAN KESIHATAN WP KUALA LUMPUR & PUTRAJAYA

Dengan hormatnya saya merujuk kepada perkara di atas dan surat puan rujukan (12)KKM/NIHSEC/P16-962 bertarikh 16 Ogos 2016 adalah berkaitan.

2. Sukacita dimaklumkan bahawa pihak kami telah meneliti permohonan puan untuk menggunakan klinik kesihatan bawah Jabatan Kesihatan Wilayah Persekutuan Kuala Lumpur & Putrajaya (seperti yang tersenarai di dalam surat permohonan) bagi tujuan penyelidikan bertajuk "***NMRR-16-1047-30685 – Contribution Of Maternal Dietary Intake During Pregnancy and Lactation And Feeding Practices On Development Of Allergic Diseases and Malnutrition In Infants At 12 Months Of Age At Selected Health Clinics In Selangor And Kuala Lumpur***" dan bersetuju memberi kebenaran penggunaan untuk menjalankan penyelidikan. Persetujuan ini tertakluk kepada perkara-perkara berikut:

2.1 Kesediaan klinik untuk berkolaborasi bagi menjalankan kajian.

2.2 Isu berkaitan perundangan adalah di bawah tanggungjawab pihak penyelidik. Oleh itu, penyelidik dinasihatkan untuk memohon insurans yang bersesuaian.

2.3 Ruang fasiliti dan keupayaan anggota adalah terhad. Oleh yang demikian, fasiliti tidak menyediakan apa-apa kemudahan termasuk pegawai atau anggota dan di klinik bagi tujuan penyelidikan ini.

Am (Tel: 03-2694 0701 Faks: 03-2694 0702 / 2693 6435 / 2697 7004 / 2698 9080), Kesihatan Awam (Faks: 03-2697 3009),
Perubatan (Faks: 03-2693 8763), Keselamatan & Kualiti Makanan (Faks: 03-2693 8760), Farmasi (Faks: 03-2693 8776)

PERMOHONAN KEBENARAN UNTUK MENJALANKAN PENYELIDIKAN DI KLINIK KESIHATAN DI BAWAH JABATAN KESIHATAN WP KUALA LUMPUR & PUTRAJAYA

2.4 Perlu mengikuti segala perundangan dan prosedur yang telah ditetapkan oleh Kerajaan Malaysia, Kementerian Kesihatan Malaysia (KKM), Pejabat Kesihatan Daerah (PKD) dan Klinik Kesihatan.

2.5 Kesemua data yang diperolehi adalah milik KKM. Mana-mana data yang diperlukan untuk sebarang tujuan pembentangan atau penerbitan perlu mendapat kelulusan bertulis Ketua Pengarah Kesihatan.

3. Untuk penjelasan lanjut, pihak tuan boleh merujuk kepada garis panduan Institut Kesihatan Negara mengenai penyelidikan di institusi dan fasiliti Kementerian Kesihatan Malaysia (Pindaan 01/2015). Perhatian dan kerjasama pihak tuan amat dihargai dan didahulukan dengan ucapan terima kasih.

Sekian.

"BERKHIDMAT UNTUK NEGARA"

Saya yang menurut perintah,

DR. WAN MANSOR BIN HAMZAH
No. Pendaftaran Penuh MPM: 25511
Pakar Perubatan Kesihatan Awam
Timbalan Pengarah Kesihatan Negeri (Kesihatan Awam)
Jabatan Kesihatan Wilayah Persekutuan
Kuala Lumpur & Putrajaya

(**DATUK DR. NARIMAH NOR BINTI YAHAYA**)
NO. MPM : 24528
Pengarah Kesihatan Negeri
Jabatan Kesihatan Wilayah Persekutuan
Kuala Lumpur & Putrajaya

s.k - Timbalan Pengarah Kesihatan Negeri (Kesihatan Awam) JKWPKL&P
- Pegawai Kesihatan Pejabat Kesihatan Kepong
- Pegawai Kesihatan Pejabat Kesihatan Titiwangsa
- Pegawai Kesihatan Pejabat Kesihatan Cheras
- Pegawai Kesihatan Pejabat Kesihatan Lembah Pantai
- Fail

Appendices

Appendix 6: Approval Letter - Hulu Langat District Health Office

PEJABAT KESIHATAN DAERAH HULU LANGAT
Lot 7523, Jalan Hentian 1C
Plaza Hentian Kajang, Jalan Reko
43000 KAJANG
SELANGOR DARUL EHSAN
MALAYSIA

Tel : 03-87367770, 03-87360614
03-87397903, 03-87397904
Faks : 03-87369687, 03-87336507
E-mel : pkd_hululangat@moh.gov.my

Ruj Kami : Bil ( ) dlm PKDHLGT
Tarikh : 8 November 2016

Dr Chin Yit Siew
Ketua Penyelidik/ Ketua Pusat Penyelidikan Kecemerlangan
Pemakanan dan Penyakit Tidak Berjangkit
Fakulti Perubatan Dan Sains Kesihatan
Universiti Putra Malaysia
43400 UPM Serdang
SELANGOR DARUL EHSAN

Puan,

MAKLUMBALAS PERMOHONAN MENJALANKAN KAJIAN "CONTRIBUTION OF MATERNAL DIETARY INTAKE DURING PREGNANCY AND LACTATION AND FEEDING PRACTICES ON DEVELOPMENT OF ALLERGIC DISEASES AND MALNUTRITIONS IN INFANTS AT 12 MONTHS OF AGE AT SELECTED HEALTH CLINICS IN SELANGOR AND KUALA LUMPUR"

Dengan segala hormatnya saya merujuk pada perkara di atas.

2. Sukacita dimaklumkan, pihak PKD Hulu Langat tiada halangan untuk membenarkan kajian dijalankan ke atas fasiliti yang dipilih oleh pihak puan. Di mohon pihak puan untuk memberikan sesalinan hasil kajian/ laporan lengkap kepada PKD Hulu Langat sebagai rujukan.

3. Kerjasama daripada pihak puan amat dihargai.

Sekian, terima kasih.

"BERKHIDMAT UNTUK NEGARA"

"BUDAYA PENYAYANG, KERJA BERPASUKAN DAN PROFESIONALISME ADALAH BUDAYA KERJA KITA"

Saya yang menurut perintah,

(DR NUR FIRDAUS BINTI MOHD RUS)
Setiausaha Jawatankuasa Penyelidikan
Pejabat Kesihatan Daerah Hulu Langat

A 317

Appendices

Appendix 7: Approval Letter - Kepong District Health Office

PEJABAT KESIHATAN DAERAH KEPONG
JALAN JINJANG PERMAI,
52000 JINJANG UTARA,
KUALA LUMPUR.

No. Tel : 03 - 6257 0352
No. Fax : 03 - 6257 0782
Emel : pkkepong@moh.gov.my

Rujukan kami : Bil (11) PKK:600-15 JLD.2
Tarikh : 30 Mei 2017

DR CHIN YIT SIEW
CIK WOON FUI CHEE
UNIVERSITY PUTRA MALAYSIA (UPM)

Tuan,

PERMOHONAN KEBENARAN UNTUK MENJALANKAN PENYELIDIKAN DI KLINIK KESIHATAN DI BAWAH PEJABAT KESIHATAN KEPONG.

Dengan segala hormatnya saya merujuk kepada perkara di atas.

2. Pihak kami tiada halangan dan memberi kebenaran untuk menjalankan penyelidikan di klinik klinik bawah penyeliaan Pejabat Kesihatan Dearah Kepong mengikut surat rujukan tuan UPM/FPSK/FRGS-2016/5524775.

3. Oleh yang demikian, untuk memudahkan kefahaman penyelidikan tersebut kami memohon satu taklimat mengenai penyelidikan tersebut diadakan pada ketetapan seperti berikut:

Tarikh:	09 Jun 2017
Masa :	10.30 pagi sehingga 12.00 tenghari
Tempat:	Bilik Mesyuarat Pejabat Kesihatan Kepong

4. Nama-nama anggota yang akan terlibat dalam taklimat tersebut seperti di lampiran A. Untuk makluman lanjut sila berhubung Dr Sundirees atas talian 012 385 6757. Kerjasama dan perhatian tuan amat dihargai dan diucapkan ribuan terima kasih.

'BERKHIDMAT UNTUK NEGARA'

Saya yang menurut perintah,

(DR .FUAD BIN HASHIM)
No. Pendaftaran Penuh MPM: 29529
Pegawai Kesihatan Daerah Kepong
Pejabat Kesihatan Daerah Kepong.
Kuala Lumpur.

Pkdk/sundirees

Appendices

Appendix 8: Information Sheet and Consent Form

JAWATANKUASA ETIKA UNIVERSITI UNTUK PENYELIDIKAN
MELIBATKAN MANUSIA (JKEUPM)
UNIVERSITI PUTRA MALAYSIA, 43400 UPM SERDANG,
SELANGOR, MALAYSIA

RESPONDENT INFORMATION SHEET AND INFORMED CONSENT FORM

1. **Title of study:** Maternal and Infant Cohort Study (MICOS) – Contribution of maternal dietary intake during pregnancy and lactation and feeding practices on development of allergic diseases, malnutrition, and cognitive development in infants at 12 months of age at selected health clinics in Selangor and Kuala Lumpur

2. **Name of investigator and institution:**

Assoc. Prof. Dr. Chin Yit Siew	Universiti Putra Malaysia
Ms. Woon Fui Chee	Universiti Putra Malaysia
Prof. Marijka Batterham	University of Wollongong
Assoc. Prof. Dr. Intan Hakimah Ismail	Universiti Putra Malaysia
Prof. Dr. Chan Yoke Mun	Universiti Putra Malaysia
Assoc. Prof. Dr. Geeta Appannah	Universiti Putra Malaysia
Assoc. Prof. Dr. Gan Wan Ying	Universiti Putra Malaysia
Dr. Amir Hamzah Abdul Latiff	Pantai Hospital Kuala Lumpur
Ms. Siti Huzaifah Bt. Mohamed Hussein	Universiti Putra Malaysia
Ms. Eva Yu Koh Xing	Universiti Putra Malaysia

3. **Name of sponsor:** Ministry of Higher Education Malaysia

4. **Introduction:**

You are invited to participate in this study because you are in your third trimester of pregnancy. The details of the study are described in this document. It is important that you understand why the research is being done and what it will involve. Please take your time to read through and consider this information carefully before you decide if you are willing to participate. Ask the researcher if anything is unclear or if you like more information. After you are properly satisfied that you understand this study, and that you wish to participate, you must sign this informed consent form.

Your participation in this study is voluntary. You do not have to be in this study if you do not want to. You may also refuse to answer any questions you do not want to answer. If you volunteer to be in this study, you may withdraw from it at any time. If you withdraw, any data collected from you up to your withdrawal will still be used for the study. Your refusal to participate or withdrawal will not affect any medical or health benefits to which you are otherwise entitled.

This study has been approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia.

5. **What is the purpose of the study?**

The purpose of this study is to determine the contribution of maternal nutritional status during pregnancy, maternal dietary intake during pregnancy and lactation, and feeding practices on development of allergic diseases, malnutrition, and cognitive development in infants at 12 months of age. This study is necessary because allergic diseases and malnutrition in children are now known as a public health concern worldwide. In Malaysia, about 1 in 5 children are at risk of developing allergies, 1 in 4 are stunted, 19.6% are underweight, 19.1% are wasted, and 6.5% are overweight. About 60.0% of allergies appear during the first year of life. Food allergy and skin allergy are the first manifestations of allergy, which usually appear during the first to second year of life. As the child growing up, allergies to food and skin allergy in children may outgrow and progress to the development of asthma and nasal allergy. Children who developed allergic diseases may exhibit stunted growth and their quality of life may be affected. In addition, poor growth or stunting in the first two years of life may lead to poor cognitive development and irreversible damage in adulthood. Hence, early life is a critical period for us to identify the causes of allergic diseases, malnutrition, and cognitive development in childrenin order to implement appropriate strategies to manage and control allergic diseases and malnutrition effectively.

A total of 533 subjects like you from 6 selected health clinics in Selangor and Kuala Lumpur will be participating in this study. The whole study will last about two years and your participation will be about one year and three months.

6. **Who should not participate in the study?**

Pregnant women who are non-Malaysian, aged less than 18 or more than 40 years old, gestational age less than 28 weeks, multiple pregnancies, delivery before 37-week gestation, with weak body defense system, planning to move out of the study area in the next one year, and fetal/newborn with birth defects.

7. **What will happen if I decide to take part?**

At third trimester of pregnancy, you will be interviewed by our trained researcher regarding your socio-demographic characteristics, family history of allergies, anaemia status, obstetrical history, sun exposure, and dietary intake during pregnancy at the health clinic. After the interview session, your blood (2mL) will be collected by a qualified blood collection personnel to determine your vitamin D level during pregnancy. After giving birth, you will be interviewed by our researcher again when you bring your child to the health clinics for regular medical check-up at 3, 6, and 12 months after birth, which are at the same time as visits for immunisation. During this interview session, you will be required to provide information on your dietary intake, sun exposure, home environment, the way you feed your child, your child's development of allergic diseases, and cognitive development. Meanwhile, your child's blood will be collected only once at 12 months old by a doctor to determine their sensitivity to a total of 36 common food and airborne substances that can trigger an allergic reaction. A blood sample of 1-2 mL will be collected from the blood vessel at the forearm of your child. During blood collection, the doctor will puncture your child's skin to withdraw blood. Once sufficient blood has been collected, a gentle pressure will be applied to your child's forearm to stop any bleeding.

8. **What are my responsibilities when taking part in this study?**

It is important that you answer all of the questions asked by the researcher honestly and completely.

9. **What will be the benefits of the study?**

(a) To you as the subject?

You will be offered a free blood test worth RM 100 to determine your vitamin D level during pregnancy. Besides that, you child will be offered a free blood test worth RM 550 to determine their sensitivity to a total of 36 common food and airborne substances that can trigger an allergic reaction. We will give you the results of you and your child's assessments and a newsletter with updates and overall group results at every follow up time point at the health clinic. With this, you will be able to identify your dietary pattern, vitamin D level, your child's development of allergic diseases, and nutritional status. In addition, we will let you know whether your child has a sensitivity to something that you didn't know about based on the results from the blood test. This information is important because it tells you whether or not your child needs to avoid eating certain foods. Meanwhile, you will be given a small gift worth RM10 at each time you completed the surveys in return for your participation.

(b) To the investigator?

The findings of the present study can provide an update concerning the prevalence of allergic diseases and malnutrition in infants. In addition, the present study can provide strong scientific evidence on the cause and effect relationship between maternal dietary intake during pregnancy and lactation and feeding practices on the development of allergic diseases, malnutrition, and cognitive development among infants. Health professionals may develop dietary practice guidelines based on the factors identified in preventing and managing allergic diseases and malnutrition among infants.

10. **What are the possible risks?**

When taking blood, you/your child may feel a sting when the needle is put in the arm (you) / heel (your child). Sometimes a small bruise can appear on the skin where the blood is taken. Apart from the mild and temporary discomfort associated with a blood test, there are no risks from contributing the blood samples.

Blood will be taken by a qualified blood collection personnel/pediatric medical officer at appropriate facilities. Since we will carry out analysis of you and your child blood, it is possible we could discover something which is of major relevance to you and your child's health, such as vitamin D deficiency and food and airborne substances sensitization. If this situation arises, we will seek advice from a medical specialist about this finding, and if they consider this finding is important to your / your child's health, we will arrange them to contact you to discuss further with you. You have a choice whether or not to be informed of these findings.

11. **What if I am injured during this study?**

If you/your child are injured as a result of being in this study, you should contact the researcher immediately. In the event of a bodily injury directly resulting from the study procedure, the researcher will report to the medical officer at the health clinic for necessary treatment. The researcher is not responsible for medical expenses due to pre-existing medical conditions, any underlying diseases, any ongoing treatment process, your negligence or willful misconduct. You do not lose any of your legal rights to seek compensation by signing this form.

12. Who is funding the research?

This study is sponsored by the Ministry of Higher Education Malaysia who will pay for all study procedures.

13. Can the research or my participation be terminated early?

The researcher may stop the study or your participation if you deliver before 37-week gestation, diagnosed with immune deficiency, planning to move out of the study area in the next one year, or your child is diagnosed with congenital abnormalities. If the study is stopped early for any reason you will be informed.

14. Will my information be kept private?

All information obtained in this study will be kept and handled in a confidential manner, in accordance with applicable laws and/or regulations. When publishing or presenting the study results, you/your child's identity will not be revealed without your expressed consent. Researchers involved in this study, qualified monitors and auditors, the sponsor or its affiliates and governmental or regulatory authorities may inspect and copy you/your child's records, where appropriate and necessary. You and your child's blood samples will be sent to laboratories for testing. The blood samples will be coded and information that can identify you/your child will be removed. Only researchers of the study will be able to link the code with you/your child.

15. Who should I call if I have questions?

If you have any questions about the study or if you think you have a study related injury and you want information about treatment, please contact:
Assoc. Prof. Dr. Chin Yit Siew (Project leader) at telephone number 03-89472680 or
Ms. Woon Fui Chee (Researcher at the site) at telephone number 016-5262192.

If you have any questions about your rights as a respondent in this study, please contact: The Secretary, Medical Research & Ethics Committee, Ministry of Health Malaysia, at telephone number 03-2287 4032.

RESPONDENT'S INFORMED CONSENT FORM

Title of study: Maternal and Infant Cohort Study (MICOS) – Contribution of maternal dietary intake during pregnancy and lactation and feeding practices on development of allergic diseases, malnutrition, and cognitive development in infants at 12 months of age at selected health clinics in Selangor and Kuala Lumpur

By signing below I confirm the following:

- I have been given oral and written information for the above study and have read and understood the information given.
- I have had sufficient time to consider participation in the study and have had the opportunity to ask questions and all my questions have been answered satisfactorily.
- I understand that my participation is voluntary and I can at any time free withdraw from the study without giving a reason. I am not taking part in any other research study at this time. I understand the risks and benefits, and I freely give my informed consent to participate under the conditions stated. I understand that I must follow the study researcher's instructions related to my participation in the study.
- I understand that study researcher, qualified monitors and auditors, the sponsor or its affiliates, and governmental or regulatory authorities, have direct access to my record in order to make sure that the study is conducted correctly and the data are recorded correctly. All personal details will be treated as STRICTLY CONFIDENTIAL.
- I will receive a copy of this respondent information sheet and informed consent form signed and dated to bring home.
- I * wish / do not wish to know the results related to my participation in the research.
  *(*delete which is not applicable)*

Respondent:

Signature: I/C number:

Name: Date:

Investigator conducting informed consent:

Signature: I/C number:

Name: Date:

Impartial witness: *(Required if respondent is illiterate and contents of respondent information sheet is orally communicated to respondent)*

Signature: I/C number:

Name: Date:

PARENT'S INFORMED CONSENT FORM

Title of study: Maternal and Infant Cohort Study (MICOS) – Contribution of maternal dietary intake during pregnancy and lactation and feeding practices on development of allergic diseases, malnutrition, and cognitive development in infants at 12 months of age at selected health clinics in Selangor and Kuala Lumpur

By signing below I confirm the following:

- I have been given oral and written information for the above study and have read and understood the information given.
- I have had sufficient time to consider my child's participation in the study and have had the opportunity to ask questions and all my questions have been answered satisfactorily.
- I understand that my child's participation is voluntary and my child can at any time free withdraw from the study without giving a reason. My child is not taking part in any other research study at this time. I understand the risks and benefits, and I freely give my informed consent to allow my child to participate under the conditions stated. I understand that my child must follow the study researcher's instructions related to my child's participation in the study.
- I understand that study researcher, qualified monitors and auditors, the sponsor or its affiliates, and governmental or regulatory authorities, have direct access to my child's record in order to make sure that the study is conducted correctly and the data are recorded correctly. All personal details will be treated as STRICTLY CONFIDENTIAL.
- I will receive a copy of this respondent information sheet and informed consent form signed and dated to bring home.
- I * wish / do not wish to know the results related to my child's participation in the research.
  *(*delete which is not applicable)*

Respondent:

Signature: I/C number:

Name: Date:

Investigator conducting informed consent:

Signature: I/C number:

Name: Date:

Impartial witness: *(Required if respondent is illiterate and contents of respondent information sheet is orally communicated to respondent)*

Signature: I/C number:

Name: Date:

JAWATANKUASA ETIKA UNIVERSITI UNTUK PENYELIDIKAN
MELIBATKAN MANUSIA (JKEUPM)
UNIVERSITI PUTRA MALAYSIA, 43400 UPM SERDANG,
SELANGOR, MALAYSIA

RISALAH MAKLUMAT DAN BORANG PERSETUJUAN RESPONDEN

Sila baca maklumat berikut dengan teliti. Sekiranya anda mempunyai sebarang pertanyaan, sila kemukakan kepada penyelidik.

1. **Tajuk Kajian:** Kajian Kohort Ibu dan Bayi (MICOS) – Sumbangan pemakanan ibu semasa mengandung dan penyusuan anak dan amalan pemberian makanan ke atas perkembangan penyakit alergi, kekurangan/kelebihan zat makanan, dan perkembangan kognitif dalam kalangan bayi pada umur 12 bulan di klinik kesihatan terpilih di Selangor dan Kuala Lumpur.

2. **Nama Institusi and Nama Penyelidik:**

Assoc. Prof. Dr. Chin Yit Siew	Universiti Putra Malaysia
Ms. Woon Fui Chee	Universiti Putra Malaysia
Prof. Marijka Batterham	University of Wollongong
Assoc. Prof. Dr. Intan Hakimah Ismail	Universiti Putra Malaysia
Prof. Dr. Chan Yoke Mun	Universiti Putra Malaysia
Assoc. Prof. Dr. Geeta Appannah	Universiti Putra Malaysia
Assoc. Prof. Dr. Gan Wan Ying	Universiti Putra Malaysia
Dr. Amir Hamzah Abdul Latiff	Pantai Hospital Kuala Lumpur
Ms. Siti Huzaifah Bt. Mohamed Hussein	Universiti Putra Malaysia
Ms. Eva Yu Koh Xing	Universiti Putra Malaysia

3. **Nama penaja:** Kementerian Pendidikan Tinggi Malaysia

4. **Pengenalan:**

Anda telah dijemput untuk menyertai penyelidikan ini kerana anda berada dalam trimester ketiga kehamilan. Risalah ini menjelaskan hal-hal berkenaan penyelidikan tersebut dengan lebih mendalam dan terperinci. Amat penting anda memahami mengapa penyelidikan ini dilakukan dan apa yang dilakukan dalam penyelidikan ini. Sila ambil masa yang secukupnya untuk membaca dan mempertimbangkan dengan teliti penerangan yang diberi sebelum anda bersetuju untuk menyertai penyelidikan ini. Jika ada sebarang kemusykilan ataupun maklumat lanjut yang anda ingin tahu, anda boleh bertanya dengan mana-mana penyelidik yang terlibat dalam penyelidikan ini. Setelah anda berpuashati bahawa anda memahami penyelidikan ini, dan anda berminat untuk turut serta, anda dikehendaki untuk menandatangani Borang Persetujuan atau Keizinan Peserta, pada muka surat akhir risalah ini.

Penyertaan anda dalam penyelidikan ini adalah secara sukarela. Anda tidak perlu menyertai penyelidikan ini jika anda tidak mahu. Anda juga mempunyai hak untuk tidak menjawab mana-mana soalan yang anda tidak mahu jawab. Anda juga boleh menarik diri daripada penyelidikan ini pada bila-bila masa sahaja. Jika anda menarik diri, segala maklumat yang telah diperolehi sebelum anda menarik diri tetap akan digunakan dalam penyelidikan ini. Jika anda tidak mahu menyertai ataupun menarik diri dari penyelidikan ini, tindakan anda tidak akan menjejaskan segala hak dan keistimewaan perubatan kesihatan yang selayaknya anda terima.

Penyelidikan ini telah mendapat kelulusan Jawatankuasa Etika dan Penyelidikan Perubatan, Kementerian Kesihatan Malaysia.

5. **Apakah tujuan penyelidikan ini dilakukan?**

Tujuan penyelidikan ini dilakukan adalah untuk menentukan sumbangan status pemakanan ibu semasa mengandung, pemakanan ibu semasa mengandung dan penyusuan anak, dan amalan pemberian makanan ke atas perkembangan penyakit alergi, kekurangan/kelebihan zat makanan, dan perkembangan kognitif dalam kalangan bayi pada umur 12 bulan. Penyelidikan ini diperlukan kerana penyakit alergi dan kekurangan/kelebihan zat makanan dalam kanak-kanak merupakan isu kesihatan awam yang kini di seluruh dunia. Di Malaysia, lebih kurang 1 daripada 5 kanak-kanak berisiko menghidapi alergi, 1 daripada 4 terbantut, 19.6% kurang berat badan, 19.1% tersusut, dan 6.5% berlebihan berat badan. Kira-kira 60.0% alergi muncul pada tahun pertama kelahiran. Alergi makanan dan alergi kulit merupakan penyakit alergi yang terbentuk paling awal di kalangan kanak-kanak, biasanya muncul pada tahun pertama hingga kedua kelahiran. Apabila kanak-kanak membesar, alergi makanan dan alergi kulit boleh berkembang menjadi asma dan alahan hidung. Kanak-kanak yang menghidapi penyakit alergi berkemungkinan besar akan mengalami tumbesaran yang terbantut dan kualiti hidup mereka akan terjejas. Di samping itu, pertumbuhan yang buruk atau terbantut dalam tempoh dua tahun pertama kehidupan boleh menyebabkan perkembangan kognitif yang lemah dan kemudaratan yang kekal dalam dewasa. Oleh itu, tahun-tahun awal kehidupan merupakan tempoh yang kritikal untuk mengenalpasti punca penyakit alergi, kekurangan/kelebihan zat makanan, dan perkembangan kognitif di kalangan kanak-kanak, supaya strategi yang sesuai boleh dilaksanakan untuk mengurus dan mengawal penyakit alergi dan kekurangan/kelebihan zat makanan secara berkesan.

Sejumlah 533 peserta seperti anda daripada 6 klinik kesihatan terpilih di Selangor dan Kuala Lumpur akan menyertai penyelidikan ini. Penyelidikan ini akan berlangsung selama dua tahun dan tempoh pembabitan anda dianggarkan selama satu tahun dan tiga bulan.

6. **Siapa yang tidak boleh menyertai penyelidikan ini?**

Ibu mengandung yang bukan merupakan warga Malaysia, berumur di bawah 18 tahun atau 40 tahun ke atas, usia kandungan kurang daripada 28 minggu, kehamilan yang leibh dari satu, bersalin sebelum minggu ke-37 kehamilan, mempunyai sistem pertahanan badan yang lemah, merancang untuk berpindah keluar dari kawasan kajian pada tahun depan,dan janin/bayi baru lahir yang mempunyai kecacatan kelahiran.

7. **Apakah yang terjadi sekiranya saya bersetuju untuk menyertai penyelidikan ini?**

Semasa kehamilan trimester ketiga., anda akan ditemuramah oleh penyelidik terlatih kami berkaitan ciri-ciri sosio-demografi, sejarah alergi keluarga, status anemia, sejarah obstetrik, pendedahan kepada matahari, dan pemakanan semasa mengandung di klinik kesihatan. Selepas sesi temuramah, darah anda (2mL) akan dikumpulkan oleh seorang staf pengambil darah yang berkelayakan untuk menentukan status vitamin D anda semasa mengandung. Selepas melahirkan anak, anda akan ditemuramah lagi oleh penyelidik kami apabila anda membawa anak anda ke klinik kesihatan untuk pemeriksaan perubatan tetap semasa 3, 6, dan 12 bulan selepas bersalin, pada masa yang sama dengan jadual lawatan untuk imunisasi. Semasa sesi temuramah ini, anda perlu memberikan maklumat mengenai pemakanan anda, pendedahan kepada matahari, persekitaran rumah anda, cara anda memberi makan kepada anak anda, perkembangan penyakit alergi, dan perkembangan kognitif anak anda. Sementara itu, darah anak anda akan diambil hanya sekali pada umur 12 bulan oleh seorang doktor untuk menentukan sensitasi mereka ke atas 36 jenis makanan biasa dan bahan bawaan udara yang boleh menyebabkan alahan. Sebanyak 1-2 mL sampel darah akan diambil daripada salur darah pada lengan anak anda. Semasa pengambilan darah, doktor akan akan mencucuk kulit anak anda untuk megambil darah. Apabila darah yang mencukupi telah dikumpulkan, tekanan akan dikenakan pada lengan anak anda untuk menghentikan pendarahan.

8. **Apakah tanggungjawab saya sewaktu menyertai penyelidikan ini?**

Amat penting anda menjawab kesemua soalan yang ditanyakan oleh penyelidik dengan jujur dan lengkap .

9. **Apakah faedah menyertai penyelidikan ini?**

(a) Kepada anda sebagai peserta?

Anda akan ditawarkan satu ujian darah percuma yang bernilai RM 100 untuk mengenalpasti status vitamin D anda semasa mengandung. Selain itu, anak anda akan ditawarkan satu ujian darah percuma yang bernilai RM 550 untuk mengenalpasti sensitasi mereka terhadap 36 jenis makanan biasa dan bahan bawaan udara yang boleh menyebabkan alahan. Kami akan memberikan anda keputusan penilaian anda dan anak anda serta satu surat berita mengenai sebarang maklumat kemaskini dan keputusan kumpulan keseluruhan pada setiap titik masa susulan di klinik kesihatan. Dengan ini, anda akan dapat mengenalpasti corak pemakanan anda, status vitamin D, perkembangan penyakit alergi, dan status pemakanan anak anda. Kami akan memaklumkan anda sama ada anak anda mempunyai sensitasi terhadap sesuatu yang anda tidak tahu berdasarkan keputusan ujian darah. Maklumat ini adalah penting kerana anda dapat mengetahui sama ada anak anda perlu mengelakkan diri daripada memakan makanan tertentu. Sementara itu, anda akan diberi hadiah kecil yang bernilai RM 10 setiap kali anda menyelesaikan kajian soal selidik sebagai penghargaan untuk penyertaan anda.

(b) Kepada penyelidik?

Penemuan kajian ini dapat memberikan maklumat mengenai prevalens penyakit alergi dan kekurangan/kelebihan zat makanan di kalangan bayi. Di samping itu, kajian ini dapat memberikan bukti saintifik yang kukuh mengenai hubungan sebab dan akibat antara pemakanan ibu semasa mengandung dan penyusuan anak dan amalan pemberian makanan ke atas perkembangan penyakit alergi, kekurangan/kelebihan zat makanan, dan perkembangan kognitif di kalangan bayi. Profesional kesihatan boleh membentukan garis panduan amalan pemakanan berdasarkan faktor yang telah dikenal pasti untuk mencegah dan mengawal penyakit alergi dan kekurangan/kelebihan zat makanan di kalangan bayi.

10. **Apakah risiko penyelidikan ini?**

Semasa mengambil darah, anda/anak anda mungkin merasakan sengatan ketika jarum dimasukkan ke dalam lengan (anda) /tumit (anak anda). Kadang-kadang lebam kecil boleh muncul di kulit di mana darah diambil. Selain daripada ketidakselesaan yang ringan dan sementara disebabkan oleh ujian darah, tiada risiko lain yang boleh berlaku akibat daripada menyumbang sampel darah. Darah akan diambil oleh staf pengambil darah/pegawai perubatan pediatrik yang berkelayakan dengan kemudahan yang bersesuaian. Disebabkan kami akan menjalankan analisis dengan menggunakan darah anda dan anak anda, terdapat kemungkinan bahawa kami mengesan sesuatu yang berkaitan dengan kesihatan anda dan anak anda, seperti kekurangan vitamin D dan sensitasi terhadap makanan dan bahan bawaan udara. Sekiranya keadaan ini berlaku, kami akan mendapatkan nasihat daripada pakar perubatan tentang penemuan ini, dan jika mereka berasa penemuan ini adalah penting terhadap kesihatan anda / anak anda, kami akan menguruskan bagi mereka untuk menghubungi dan berbincang dengan anda. Anda mempunyai pilihan sama ada anda ingin dimaklumkan mengenai penemuan ini.

11. **Apakah yang akan terjadi sekiranya saya tercedera semasa menyertai kajian ini?**

Jika anda/anak anda tercedera kerana penyertaan anda/anak anda dalam penyelidikan ini, anda haruslah menghubungi penyelidik dengan segera. Sekiranya kecederaan fizikal/badan terhasil secara langsung akibat daripada prosedur penyelidikan, penyelidik akan melaporkan kepada pegawai perubatan di klinik kesihatan untuk memberi rawatan yang diperlukan. Tetapi pihak penyelidik tidak akan bertanggungjawab terhadap perbelanjaan perubatan bagi penyakit atau rawatan yang telah wujud sebelum penyertaan anda/anak anda dalam penyelidikan ini, ataupun mana-mana proses rawatan yang sedang anda/anak anda

ikuti, ataupun sebarang masalah yang timbul sama ada daripada kecuaian anda sendiri atau salah laku yang disengajakan. Walaubagaimanapun, anda tetap tidak kehilangan mana-mana hak anda di sisi undang-undang untuk mendapatkan pampasan sekalipun anda sudah menandatangani borang ini.

12. Siapakah yang membiayai penyelidikan ini?

Kajian ini ditaja sepenuhnya oleh Kementerian Pendidikan Tinggi Malaysia yang akan membayar semua prosedur penyelidikan yang berkaitan.

13. Bolehkah penyelidikan ataupun penyertaan saya ditamatkan lebih awal daripada yang dirancang?

Penyelidik boleh menamatkan penyelidikan ini ataupun menamatkan penyertaan anda dalam penyelidikan ini sekiranya anda bersalin sebelum minggu ke-37 kehamilan, disahkan menghadapi masalah kekurangan imun, merancang untuk berpindah keluar dari kawasan kajian pada tahun depan, atau anak disahkan mempunyai keabnormalan kongenital. Jika penyelidikan ini dihentikan terlebih awal, di atas sebab-sebab tertentu, anda akan dimaklumkan.

14. Adakah maklumat saya akan dirahsiakan ?

Segala maklumat yang diperolehi dalam penyelidikan ini akan disimpan dan dikendalikan secara sulit, bersesuaian dengan peraturan-peraturan dan/ atau undang-undang yang berkenaan. Sekiranya hasil penyelidikan ini diterbitkan atau dibentangkan kepada orang ramai, identiti anda/anak anda tidak akan didedahkan tanpa kebenaran anda terlebih dahulu. Pihak-pihak tertentu seperti penyelidik yang terlibat dalam penyelidikan ini, juruaudit dan jurupantau yang terlatih, pihak penaja atau pihak gabungannya, pihak berkuasa kerajaan atau undang-undang, boleh memeriksa dan membuat salinan laporan anda/anak anda jika berkenaan dan diperlukan. Sampel darah anda dan anak anda akan dihantar ke makmal untuk diuji. Sampel darah tersebut akan dikodkan dan maklumat yang boleh mengenal pasti identiti anda/anak anda akan dikeluarkan. Hanya penyelidik dalam penyelidikan ini sahaja yang dapat menghubungkan kod tersebut dengan identiti anda/anak anda.

15. Siapakah yang perlu saya hubungi sekiranya saya mempunyai sebarang pertanyaan?

Sekiranya anda mempunyai sebarang pertanyaan mengenai penyelidikan ini atau jika anda mengesyaki anda mengalami kecederaan yang terhasil daripada penyelidikan ini dan anda mahukan maklumat tentang rawatannya, anda boleh menghubungi:
Dr. Chin Yit Siew (Ketua projek) pada sambungan telefon 03-89472680 atau
Cik Woon Fui Chee (Penyelidik di tempat kajian) pada sambungan telefon 016-5262192.

Jika anda mempunyai sebarang pertanyaan berkaitan dengan hak-hak anda sebagai peserta dalam penyelidikan ini, sila hubungi: Setiausaha, Jawatankuasa Etika & Penyelidikan Perubatan, Kementerian Kesihatan Malaysia, melalui talian telefon 03-2287 4032.

BORANG PERSETUJUAN RESPONDEN

Tajuk Kajian: Kajian Kohort Ibu dan Bayi (MICOS) – Sumbangan pemakanan ibu semasa mengandung dan penyusuan anak dan amalan pemberian makanan ke atas perkembangan penyakit alergi, kekurangan/kelebihan zat makanan, dan perkembangan kognitif dalam kalangan bayi pada umur 12 bulan di klinik kesihatan terpilih di Selangor dan Kuala Lumpur.

Dengan menandatangani di bawah, saya mengesahkan bahawa :

- Saya telah diberi maklumat tentang penyelidikan di atas secara lisan dan bertulis and saya telah membaca dan memahami segala maklumat yang diberikan dalam risalah ini.
- Saya telah diberikan masa yang secukupnya untuk mempertimbangkan penyertaan saya dalam penyelidikan ini dan telah diberi peluang untuk bertanyakan soalan dan semua persoalan saya telah dijawab dengan sempurna dan memuaskan.
- Saya juga faham bahawa penyertaan saya adalah secara sukarela dan pada bila-bila masa saya bebas menarik diri daripada penyelidikan ini tanpa harus memberi sebarang alasan. Saya tidak mengambil bahagian dalam mana-mana penyelidikan lain pada masa ini. Saya juga memahami tentang risiko dan manfaat penyelidikan ini dan saya secara sukarela memberi persetujuan untuk menyertai penyelidikan ini di bawah syarat-syarat yang telah dinyatakan di atas. Saya faham saya harus mematuhi nasihat dan arahan yang berkaitan dengan penyertaan saya dalam penyelidikan ini daripada penyelidik kajian ini.
- Saya faham bahawa penyelidik kajian ini, pemantau dan juruaudit terlatih, pihak penaja atau gabungannya, dan pihak berkuasa kerajaan atau undang-undang, mempunyai akses langsung dan boleh menyemak laporan saya bagi memastikan penyelidikan ini dijalankan dengan betul dan data direkodkan dengan betul. Segala maklumat dan data peribadi akan dianggap sebagai SULIT.
- Saya akan menerima satu salinan 'Risalah Maklumat dan Borang Persetujuan Responden' yang telah lengkap dengan tarikh dan tandatangan untuk dibawa pulang ke rumah.
- Saya * ingin / tidak ingin mengetahui keputusan yang berkaitan dengan penyertaan saya dalam kajian ini. *(*Potong mana yang tidak berkenaan)*

Responden:

Tandatangan: Nombor K/P:

Nama: Tarikh :

Penyelidik yang mengendalikan proses menandatangani borang keizinan:

Tandatangan: Nombor K/P:

Nama: Tarikh :

Saksi tidak-berpihak/adil: *(Diperlukan; jika responden adalah buta huruf dan kandungan risalah maklumat responden disampaikan secara lisan kepada responden)*

Tandatangan: Nombor K/P:

Nama: Tarikh :

BORANG PERSETUJUAN IBU BAPA

Tajuk Kajian: Kajian Kohort Ibu dan Bayi (MICOS) – Sumbangan pemakanan ibu semasa mengandung dan penyusuan anak dan amalan pemberian makanan ke atas perkembangan penyakit alergi, kekurangan/kelebihan zat makanan, dan perkembangan kognitif dalam kalangan bayi pada umur 12 bulan di klinik kesihatan terpilih di Selangor dan Kuala Lumpur.

Dengan menandatangani di bawah, saya mengesahkan bahawa :

- Saya telah diberi maklumat tentang penyelidikan di atas secara lisan dan bertulis and saya telah membaca dan memahami segala maklumat yang diberikan dalam risalah ini.
- Saya telah diberikan masa yang secukupnya untuk mempertimbangkan penyertaan anak saya dalam penyelidikan ini dan telah diberi peluang untuk bertanyakan soalan dan semua persoalan saya telah dijawab dengan sempurna dan memuaskan.
- Saya juga faham bahawa penyertaan anak saya adalah secara sukarela dan pada bila-bila masa anak saya bebas menarik diri daripada penyelidikan ini tanpa harus memberi sebarang alasan. Anak saya tidak mengambil bahagian dalam mana-mana penyelidikan lain pada masa ini. Saya juga memahami tentang risiko dan manfaat penyelidikan ini dan saya secara sukarela memberi persetujuan untuk membenarkan anak saya menyertai penyelidikan ini di bawah syarat-syarat yang telah dinyatakan di atas. Saya faham anak saya harus mematuhi nasihat dan arahan yang berkaitan dengan penyertaan anak saya dalam penyelidikan ini daripada penyelidik kajian ini.
- Saya faham bahawa penyelidik kajian ini, pemantau dan juruaudit terlatih, pihak penaja atau gabungannya, dan pihak berkuasa kerajaan atau undang-undang, mempunyai akses langsung dan boleh menyemak laporan anak saya bagi memastikan penyelidikan ini dijalankan dengan betul dan data direkodkan dengan betul. Segala maklumat dan data peribadi akan dianggap sebagai SULIT.
- Saya akan menerima satu salinan 'Risalah Maklumat dan Borang Persetujuan Responden' yang telah lengkap dengan tarikh dan tandatangan untuk dibawa pulang ke rumah.
- Saya * ingin / tidak ingin mengetahui keputusan yang berkaitan dengan penyertaan anak saya dalam kajian ini. *(*Potong mana yang tidak berkenaan)*

Responden:

Tandatangan: Nombor K/P:

Nama: Tarikh :

Penyelidik yang mengendalikan proses menandatangani borang keizinan:

Tandatangan: Nombor K/P:

Nama: Tarikh :

Saksi tidak-berpihak/adil: *(Diperlukan; jika responden adalah buta huruf dan kandungan risalah maklumat responden disampaikan secara lisan kepada responden)*

Tandatangan: Nombor K/P:

Nama: Tarikh :

Appendices

Appendix 9: Comparison of characteristics of study respondents between the final cohort with loss to follow up

Variable	Final cohort at 12 months (n = 380)	Loss to follow up (n =155)	p-value
Maternal characteristics			
Maternal age (year)	30.1 ± 4.2	29.6 ± 4.0	0.225
Maternal ethnicity			0.952
Malay	350 (92.1)	143 (92.3)	
Non-Malay	30 (7.9)	12 (7.7)	
Maternal educational level			0.824
Secondary	68 (17.9)	29 (18.7)	
Tertiary	312 (82.1)	126 (81.3)	
Maternal work status			0.387
Working	267 (70.3)	103 (66.5)	
Non-working	113 (29.7)	52 (33.5)	
Monthly household income [a]			0.003*
Low (< RM 2300)	52 (13.7)	40 (25.8)	
Moderate (RM 2300-5599)	209 (55.0)	72 (46.5)	
High (> RM 5600)	119 (31.3)	43 (27.7)	
Obstetrical history			
Parity			0.208
Primiparous	154 (40.5)	72 (46.5)	
Multiparous	226 (59.5)	83 (53.5)	
Pre-pregnancy BMI			0.263
Underweight (< 18.5 kg/m^2)	30 (7.9)	18 (11.6)	
Normal weight (18.5-24.9 kg/m^2)	204 (53.7)	86 (55.5)	
Overweight/obese (≥ 25.0 kg/m^2)	146 (38.4)	51 (32.9)	
Gestational weight gain			0.685
Inadequate	117 (30.8)	53 (34.2)	
Adequate	151 (39.7)	61 (39.4)	
Excessive	112 (29.5)	41 (26.5)	
Family history of allergic disease			0.328
No	123 (32.4)	57 (36.8)	
Yes	257 (67.6)	98 (63.2)	
Maternal vitamin D status during late pregnancy			0.186
Deficiency (< 30 noml/L)	164 (43.2)	63 (40.6)	
Insufficiency (30-49.9 nmol/L)	181 (47.6)	84 (54.2)	
Sufficiency (≥ 50 nmol/L)	35 (9.2)	8 (5.2)	

Data shown are mean ± standard deviation for continuous variables and number (percentage) of respondents for categorical variables. P-values for difference were determined by Chi-square test for categorical variables and Independent T-Test for two independent samples. RM, Ringgit Malaysia (1 US dollar = RM 4.09 (as of March 24, 2020).

Appendix 10: Questionnaire

Reference number / No. Rujukan / 编号: _____

FACULTY OF MEDICINE AND HEALTH SCIENCES
DEPARTMENT OF NUTRITION AND DIETETICS

FAKULTI PERUBATAN DAN SAINS KESIHATAN
JABATAN PEMAKANAN DAN DIETETIK

博特拉大学
医学与保健科学系院
营养与饮食治疗部门

QUESTIONNAIRE (THIRD TRIMESTER)
BORANG SOAL SELIDIK (TRIMESTER KETIGA)
問卷(妊娠第三期)

Contribution of maternal vitamin D status during pregnancy and feeding practices on development of allergic diseases and malnutrition in infants at 12 months of age in Selangor and Kuala Lumpur
Sumbangan pemakanan ibu semasa mengandung dan penyusuan anak dan amalan pemberian makanan ke atas perkembangan penyakit alergi dan kekurangan/kelebihan zat makanan dalam kalangan bayi pada umur 12 bulan di klinik kesihatan terpilih di Selangor dan Kuala Lumpur
雪兰莪州和吉隆坡特定诊所怀孕期和哺乳期的饮食和喂养方式对婴儿在12个月大时过敏性疾病和营养不良发展的贡献

Researchers / Penyelidik / 研究人员:
Dr. Chin Yit Siew (Project Leader / Ketua Projek / 项目负责人)
Assoc. Prof. Dr. Intan Hakimah Ismail
Assoc. Prof. Dr. Chan Yoke Mun
Dr. Geeta Appannah
Dr. Gan Wan Ying
Woon Fui Chee

Note: All information provided is confidential and only for research purposes. Your honesty and sincerity in providing information is much appreciated. Thank you in advance for your cooperation.

Nota: Segala maklumat yang diberikan adalah sulit dan hanya untuk tujuan penyelidikan sahaja. Kejujuran dan keikhlasan anda dalam memberikan maklumat adalah amat diharapkan. Segala kerjasama yang diberikan amat dihargai dan didahului dengan ucapan jutaan terima kasih.

注意：所有提供的资料将被保密和只会被用于此项研究而已。我们希望您能提供确实的资料。对于您的配合, 我们给予万二分的感谢。

Part A: Respondent's information / Bahagian A: Maklumat responden / A项：参与者资料

1	Age (year) / Umur 年龄 / (Tahun 岁)	
2	Date of birth (date/month/year) Tarikh lahir (hari/bulan/tahun) 出生日期(日/月/年)	
3	Ethnicity / Etnik/ 种族	a) Malay / Melayu / 巫裔 b) Chinese / Cina / 华裔 c) Indian / India / 印裔 d) Others / Lain-lain / 其他 (Please specify / Sila nyatakan / 请说明: _____)
4	Occupation / Pekerjaan / 职业	
5	Highest education level Tahap pendidikan tertinggi 最高学历	a) No formal education / Tiada pendidikan formal / 没有正规教育 b) Primary school / Sekolah rendah / 小学 (1 ，2 ，3 ，4 ，5 ，6) c) Secondary school / Sekolah menengah / 中学 (1 ，2 ，3 ，4 ，5) d) STPM/Diploma/A level / 预科, 文凭, 证书 e) Bachelor's degree / Ijazah sarjana muda / 学士学位 f) Master degree / Ijazah sarjana / 硕士学位 g) Doctor of Philosophy / Doktor falsafah / 博士
6	Marital status / Status perkhawinan 婚姻状况	a) Single / Bujang / 单身 b) Married / Berkahwin / 已婚 c) Divorced / Bercerai / 离婚 d) Widowed / Balu / 丧偶
7	Monthly household income Jumlah pendapatan isi rumah sebula 家庭每月总收入	a) < RM 2300 b) RM 2300 – 5599 c) > RM 6000 – 5600
8	Current gestatinal age (week) / Minggu kehamilan ini / 目前怀孕周数	
9	Number of previous pregnancies / Bilangan kehamilan sebelum ini / 之前的怀孕次数	
10	Number of children / Bilangan anak / 拥有几位孩子	
11	Prepregnancy weight / Berat pra-kehamilan / 怀孕前体重 (kg)	
12	Height / Ketinggian / 身高 (cm)	
13	Last measured weight Ukuran berat badan terakhir 最后一次测量的体重 (kg)	
13	Have you consumed antibiotics during this pregnancy? Pernahkah anda makan antibiotik selama kehamilan ini? 怀孕期间您服用过抗生素吗？	

Part B: Family history of allegy / Bahagian B: Sejarah alergi keluarga / B项：家族过敏史

Have you or your family members had any of the following allergic diseases? / Adakah anda atau ahli keluarga anda mempunyai mana-mana penyakit alergi yang berikut? / 您或您的家人有任何以下过敏性疾病吗？

Allergic Disease **Penyakit alergi** **过敏性疾病**	**You** **Anda** **您**	**Your Husband** **Suami anda** **您的丈夫**	**Your Child / Anak anda / 您的孩子 (except child in this study / anak selain daripada kajian ini / 此研究以外的孩子)**
Food allergy / Alergi makanan / 食物过敏 Had rash in the skin and sickness within two hours of eating some food and the symptoms repeated each time the same food was eaten. Mempunyai ruam merah di kulit atau sakit dalam masa dua jam selepas makanan makanan tertentu dan simptom-simptom ini berulang setiap kali makanan yang sama dimakan 在吃了特定的食物后的2小时内出现红疹或症状及这些症状在每一次食用同样的食物时重复发生 What food that your allergy to? Makanan yang anda alergi? 您对什么食物过敏？	a) No / Tidak否 b) Yes /Ya有 _____	a) No / Tidak否 b) Yes /Ya有 _____	a) No / Tidak否 b) Yes /Ya有 _____
Eczema / Ekzema / 湿疹 Had itchy skin condition that affect the skin creases such as fronts of elbows, behind the knees, fronts of ankles, around the neck, or eyes Mempunyai ruam gatal yang menjejaskan lipatan kulit seperti depan siku, belakang lutut, bahagian depan buku lali, di sekitar kawasan leher atau mata 在皮肤皱褶处如肘弯处, 膝关节后方 ,踝关节前方,脸颊，颈部或眼睛周围有瘙痒的情况	a) No / Tidak否 b) Yes /Ya有	a) No / Tidak否 b) Yes /Ya有	a) No / Tidak否 b) Yes /Ya有
Asthma / Asma / 哮喘 Had symptoms such as coughing, wheezing, chest tightness, and shortness of breath Mempunyai simptom seperti batuk, berdehit, lelah di dada, dan sesak nafas 出现诸如咳嗽，喘息，胸闷和呼吸急促等症状	a) No / Tidak否 b) Yes /Ya有	a) No / Tidak否 b) Yes /Ya有	a) No / Tidak否 b) Yes /Ya有
Rhinitis / Rhinitis / 鼻炎 Had symptoms such as runny nose, sneezing, itching, and watery eyes after exposure to specific substances such as dust, animal hair, and pollen Mempunyai simptom seperti hidung berair, bersin, gatal-gatal, dan mata berair selepas terdedah kepada bahan tertentu seperti habuk, bulu binatang, debunga 接触如灰尘，动物毛发和花粉之类的特定物后出现流鼻涕，打喷嚏，瘙痒和流泪的症状	a) No / Tidak否 b) Yes /Ya有	a) No / Tidak否 b) Yes /Ya有	a) No / Tidak否 b) Yes /Ya有

Part C：Food Habit / Bahagian B：Amalan Pemakanan / B项：饮食习惯。

1. In this section, respondents will be asked questions on whether they have eaten or not the type of foods listed over the past one month. Write down numbers in the column how many times were consumed Daily, Weekly Monthly, or Never/Less than once per month.

   Dalam bahagian ini, responden akan ditanya soalan terbuka sama ada pernah atau tidak makan makanan yang telah disenaraikan dalam sebulan yang lepas. Tuliskan angka dalam kolum bilangan kali diambil samada dalam **Per Hari** atau **Per Minggu** atau **Per Bulan** atau **Tidak pernah / Kurang Dari Sekali Sebulan.** (Pastikan hanya satu kolum sahaja yang diisi).

   在本项中，参与者将被询问是否曾在过去的一个月中吃过列出的食品。请在食用次数的空格内填入号码，如**每天几次**或**每周几次**或**每月几次**或**不曾/一个月少于一次**。(确保只填入一格)。

2. How many times each serving were taken refers to how many of those foods were eaten by the respondents for each time.

   Berapa banyak sajian setiap kali makan merujuk kepada bilangan hidangan yang diambil setiap kali makan.

   每次食用多少分量是指每次用餐所吃食物的分量。

3. Every type of food has been given their appropriate meal measurement according to “Malaysian Food Serving Size Album” and also a list of weight of these foods in household measurement. These meal measurements were based on regular size. Interviewer need to show the food photos or standard food measurement tools (provided) to the respondents for each meal.

   Setiap jenis makanan telah diberikan ukuran hidangan tertetu berpandukan “Album Saiz Sajian Makanan Malaysia” dan juga senarai berat makanan dalam ukuran isirumah. Ukuran hidangan ini adalah berdasarkan saiz sederhana. Penemu ramah hendaklah menunjukkan gambar makanan atau alat sukatan makanan (yang dibekalkan) kepada responden bagi setiap hidangan.

   每种食品已被给予根据“马来西亚食物份量专辑”的特定食份量和根据此项食品重量的份量。此份量是根据中等尺寸的份量。访问者须提供参与者每种份量的食品图片或食品测量器。

No.	Type of food Jenis makanan 食物种类	How frequent each food was taken Berapa kali kekerapan pengambilan dalam 每种食物食用次数				Reference of meal size Rujukan saiz hidangan 份量参考	Total servings each time eaten Jumlah sajian setiap kali makan 每次食用份量
		Daily Sehari 每日	Weekly Seminggu 每周	Monthly Sebulan 每月	Never/ less than once per month Tidak pernah / < sekali sebulan 不曾/一个月少于一次		
1	**Fortified food / Makanan yang diperkaya / 强化食品**						
a	Bread/Roti/面包 Brand/Jenama/ 牌子: _____					Slices Keping片	
b	Cereal without milk/Bijirin tanpa susu/不加奶麦片 Brand/Jenama/ 牌子: _____					Tablespoon Sudu makan 汤匙	
c	Milk with cereal (3 in 1) Susu bersama bijirin (3 in 1) 牛奶加麦片(3合1) Brand/Jenama/ 牌子: _____					Cup / Cawan杯	
d	Waffle / Wafel松饼					Piece / Keping 片	
e	Pancake / Lempeng薄煎饼					Piece / Keping 片	
f	Lasagna, spaghetti with cheese Lasagna, spaghetti dengan keju 烤宽面条，奶酪意粉					Bowl Mangkuk碗	
g	Mashed potatoes with milk and margarine/Kentang Lenyek薯泥					Small container Bekas kecil小盒	
h	Fortified soy drink / Minuman soya diperkaya强化大豆饮料 Brand/Jenama/ 牌子: _____					Cup / Cawan杯	
i	Full cream milk powder / Susu tepug penuh krim全脂奶粉 Brand/Jenama/ 牌子: _____					Tablespoon Sudu makan 汤匙 Scoop / Skup舀	
j	Low fat milk powder / Susu tepung rendah lemak低脂奶粉 Brand/Jenama/ 牌子: _____					Tablespoon Sudu makan 汤匙 Scoop	
k	Skim milk powder / Susu tepung skim tanpa lemak脱脂奶粉 Brand/Jenama/ 牌子: _____					Tablespoon Sudu makan 汤匙 Scoop / Skup舀	
l	Milk powder for pregnant women / Susu tepung ibu mengandung 孕妇奶粉 Brand/Jenama/ 牌子: _____					Scoop / Skup舀	
m	Malt milk powder Susu tepung malt麦芽奶粉 Brand/Jenama/ 牌子: _____					Tablespoon Sudu makan 汤匙	
n	Full cream milk Susu penuh krim 全脂牛奶 Brand/Jenama/ 牌子: _____					Cup / Cawan杯 Glass / Gelas杯	
o	Low fat milk Susu rendah lemak 低脂牛奶 Brand/Jenama/ 牌子: _____					Cup / Cawan杯 Glass / Gelas杯	
p	Skim milk / Susu skim tanpa lemak 脱脂牛奶 Brand/Jenama/ 牌子: _____					Cup / Cawan杯 Glass / Gelas杯	
q	Fresh milk / Susu segar鲜奶 Brand/Jenama/ 牌子: _____					Cup / Cawan杯 Glass / Gelas杯	
r	Flavoured milk Susu berperisa调味牛奶 Brand/Jenama/ 牌子: _____					Cup / Cawan杯 Glass / Gelas杯	
s	Condensed milk Susu pekat manis炼乳 Brand/Jenama/ 牌子: _____					Tablespoon Sudu makan 汤匙	
t	Yogurt 酸奶 Brand/Jenama/ 牌子: _____					Cup / Cawan杯 Container Bekas盒	
u	Milk dessert (pudding/custard) Pencuci mulut yang diperbuat daripada susu (puding/kastard) 奶制甜品(布丁/奶黄)					Scoop / Skup舀 Cup / Cawan杯	
v	Glucose drink fortified with vitamin D / Minuman glukosa yang diperkaya dengan vitamin					Tablespoon Sudu makan 汤匙	

	D维生素D强化葡萄糖饮料						
w	Homemade ice cream made from milk / Aiskrim yang diperbuat sendiri dari susu自制牛奶雪糕					Slices / Potong 片 Scoop / Skup舀	
x	Butter / Mentega牛油					Teaspoon Sudu teh茶匙	
y	Margarine / Marjerin人造奶油					Teaspoon Sudu teh茶匙	
2	**Natural Food / Makanan semulajadi / 天然食物**						
a	Canned sardines Sardin tin罐头沙丁鱼					Piece / Ekor条	
b	Canned tuna Tuna tin罐头金枪鱼					tbsp汤匙	
c	Canned mackerel / Mackerel dalam tin罐头鲭鱼					Piece / Ekor条	
d	Eastern little tuna Ikan tongkol金枪鱼					Piece / Ekor条	
e	Indian mackerel Ikan kembong鲭鱼					Piece / Ekor条	
f	Spanish mackerel Ikan tenggiri马鲛鱼					Slice / Potong 片	
g	Sardine / Ikan sardin沙丁鱼					Piece / Ekor条	
h	Salmon / Ikan salmon三文鱼					Slice / Potong 片	
i	Anchovies / Ikan bilis江鱼仔					tbsp汤匙	
j	Prawn / Udang虾					Piece / Ekor只	
k	Shrimp / Udang kecil小虾					tbsp汤匙	
l	Chicken / Ayam鸡肉					Piece / Ketul块	
m	Beef / Daging lembu牛肉					Matchbox Kotakmancis 火柴盒	
n	Pork / Daging babi猪肉					Matchbox Kotakmancis 火柴盒	
o	Beef sausage / Sosej lembu 牛肉香肠					Piece/Keping块	
p	Pork sausage / Sosej babi 猪肉香肠					Piece/Keping块	
q	Chicken liver / Hati ayam鸡肝					Piece / Ketul块	
r	Cow liver / Hati lembu牛肝					Piece / Ketul块	
s	Eggs / Telur蛋					Whole / Biji粒	
t	Mushroom / Cendawan蘑菇					Cup / Cawan杯	
3	**Dietary supplements / Supplemen营养补充剂**						
a	Cod liver oil / Minyak hati ikan cod鱼肝油 Brand / Jenama牌子: _____					Pill / Biji粒 tbsp汤匙	
b	Fish oil / Minyak ikan鱼油 Brand / Jenama牌子: _____					Pill / Biji粒 tbsp汤匙	
c	New Obimin					Pill / Biji粒	
d	Obimin Plus					Pill / Biji粒	
e	Pramilet					Pill / Biji粒	
f	Iberet folic					Pill / Biji粒	
g	Vitamin D维生素D Brand / Jenama牌子: _____					Pill / Biji粒	
h	Multivitamin多种维生素 Brand / Jenama牌子: _____					Pill / Biji粒	
i	Calcium with vitamin D Kalsium dengan vitamin D 维生素D钙补充剂 Brand / Jenama牌子: _____					Pill / Biji粒	
j	Calcium / Kalsium钙 Brand / Jenama牌子: _____					Pill / Biji粒	
k	Vitamin C维生素C					Pill / Biji粒	
l	Vitamin B Complex 综合维生素B					Pill / Biji粒	
m	Folic acid / Asid folik叶酸					Pill / Biji粒	
n	Others / Lain-lain其他 Brand / Jenama牌子: _____					Pill / Biji粒 tbsp汤匙	

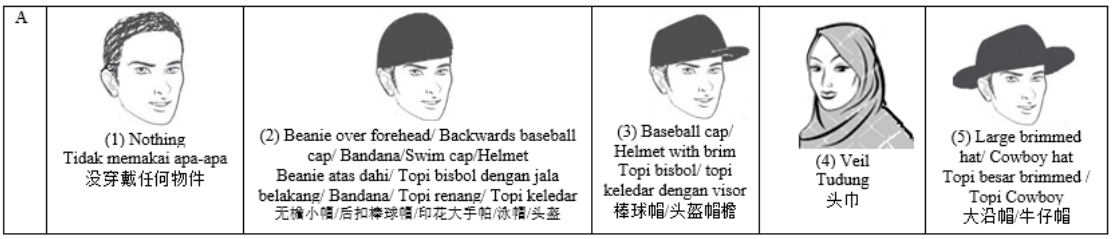
Part D：Sun Exposure Log / Bahagian H：Log Pendedahan kepada Matahari / H项：日晒日志

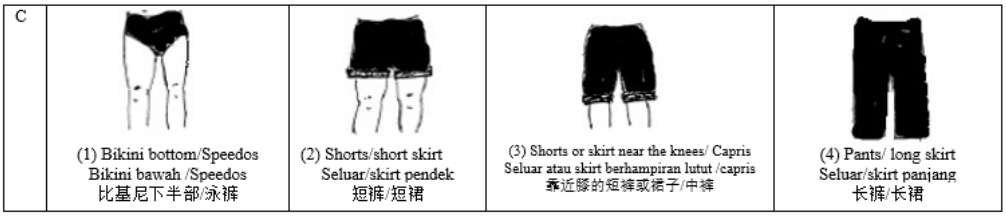
1. Recall how long you were outdoors during each time period if it is greater than 5 mins. / Sila imbas kembali berapa lama anda berada di luar pada setiap tempoh masa jika ia melebihi 5 minit. 如果您在户外的时间超过5分钟以上，请回想您每个时段在户外的总共时间。
2. Record your outdoor activity next to the appropriate time period. / Sila rekodkan aktiviti luar yang anda lakukan pada tempoh masa yang sesuai. 请在相应的时间段记录您的户外活动。
3. Record which parts of your body were exposed to the sun or covered with sunscreen using the key provided. (Please refer to the attached clothing key). Sila rekodkan bahagian badan anda yang terdedah kepada matahari atau disapu dengan krim pelindung matahari dengan menggunakan gambar yang disediakan. (Sila rujuk gambar berpakaian yang dilampirkan). 请使用所提供的图片记录您暴露在阳光下或使用防晒霜掩遮的身体部位。(请参考附件衣着图片)

Time Masa 时间	Outdoor activity Aktiviti luar 户外活动	Time spent outdoors (mins) Masa di luar (minit) 在户外的时间(分钟)	Frequency days/week Kekerapan hari/seminggu 次数 天/一周	Are you using? Adakah anda gunakan? 您是否使用？		Clothing Pakaian服装				Sunscreen / Pelindung matahari防晒霜				SPF
				Glove / Sarung tangan手套	Umbrella Payung雨伞	A	B	C	D	A	B	C	D	
7am-8am			__ / 7											
8am-9am			__ / 7											
9am-10am			__ / 7											
10am-11am			__ / 7											
11am-12pm			__ / 7											
12pm-1pm			__ / 7											
1pm-2pm			__ / 7											
2pm-3pm			__ / 7											
3pm-4pm			__ / 7											
4pm-5pm			__ / 7											
5pm-6pm			__ / 7											
6pm-7pm			__ / 7											

Clothing Key / Gambar Berpakaian / 衣着图片

Pick a number from each area A-D that best represents what you're wearing (or where you've put on the sunscreen for the exposed skin):
Pilih satu nombor dari setiap bahagian A hingga D yang paling mewakili apa yang anda pakai (atau bahagian badan yang terdedah kepada matahari yang telah menyapu krim pelindung matahari) 请从每项A至D选择一个最能代表您穿着的号码(或您暴露在阳光下已涂防晒霜的身体部位)：





Reference number / No. Rujukan / 编号: _____

FACULTY OF MEDICINE AND HEALTH SCIENCES
DEPARTMENT OF NUTRITION AND DIETETICS

FAKULTI PERUBATAN DAN SAINS KESIHATAN
JABATAN PEMAKANAN DAN DIETETIK

博特拉大学
医学与保健科学系院
营养与饮食治疗部门

QUESTIONNAIRE (3, 6, 12 MONTHS)
BORANG SOAL SELIDIK (BULAN KE-3, 6, 12)
問卷(3, 6, 12个月）

Contribution of maternal vitamin D status during pregnancy and feeding practices on development of allergic diseases and malnutrition in infants at 12 months of age in Selangor and Kuala Lumpur
Sumbangan pemakanan ibu semasa mengandung dan penyusuan anak dan amalan pemberian makanan ke atas perkembangan penyakit alergi dan kekurangan/kelebihan zat makanan dalam kalangan bayi pada umur 12 bulan di klinik kesihatan terpilih di Selangor dan Kuala Lumpur
雪兰莪州和吉隆坡特定诊所怀孕期和哺乳期的饮食和喂养方式对婴儿在12个月大时过敏性疾病和营养不良发展的贡献

Researchers / Penyelidik / 研究人员:
Dr. Chin Yit Siew (Project Leader / Ketua Projek / 项目负责人)
Assoc. Prof. Dr. Intan Hakimah Ismail
Assoc. Prof. Dr. Chan Yoke Mun
Dr. Geeta Appannah
Dr. Gan Wan Ying
Woon Fui Chee

Note: All information provided is confidential and only for research purposes. Your honesty and sincerity in providing information is much appreciated. Thank you in advance for your cooperation.

Nota: Segala maklumat yang diberikan adalah sulit dan hanya untuk tujuan penyelidikan sahaja. Kejujuran dan keikhlasan anda dalam memberikan maklumat adalah amat diharapkan. Segala kerjasama yang diberikan amat dihargai dan didahului dengan ucapan jutaan terima kasih.

注意：所有提供的资料将被保密和只会被用于此项研究而已。我们希望您能提供确实的资料。对于您的配合, 我们给予万二分的感谢。

Part A: Child's information / Bahagian A: Maklumat anak (A项：孩子的资料)		
1	Child's date of birth (date/month/year) Tarikh lahir anak (hari/bulan/tahun) 孩童出生日期(日/月/年)	___ / ___ / ___
2	Child's sex / Jantina anak孩童性别	a. Male / Lelaki男 b. Female / Perempuan女
3	Child's mode of delivery Jenis kelahiran anak 孩童出生方式	a. Vaginal delivery / Kelahiran normal 自然分娩 b. Caesarean section delivery Pembedahan Caesarean剖腹产 c. Others / Lain-lain 其他 (Please state / sila nyatakan请说明: _____)
4	Gestation age at birth Minggu gestasi semasa kelahiran出生胎龄	_____ week / minggu 周
5	Child's anthropometric measurements **at birth** Ukuran antropometrik anak **ketika lahir** 孩童**出生时**的人体测量	Length / Panjang长度 : _____ cm Weight / Berat badan体重 : _____ kg
6	Child's **current** anthropometric measurements Ukuran antropometrik anak **sekarang** 孩童**现在**的人体测量	Date / Tarikh 日期 : _____ Length Panjang长度 : _____ cm Weight / Berat badan体重 : _____ kg

Part B：Environmental exposure / Bahagian B：Pendedahan alam sekitar / B项：环境接触

1. How many siblings does your child has? Berapa orangkah abang dan kakak yang anak anda ada? 您的孩子有几位哥哥和姐姐?

_____siblings / orang abang dan kakak 位哥哥和姐姐

2. In the past 3 months, have you had a pet at home? Dalam tempoh 3 bulan yang lepas, adakah anda mempunyai haiwan peliharaan di rumah?
在过去的3个月内，您的家里有养宠物吗?

a. Yes / Ya 是 b. No / Tidak 否

If **Yes** / Jika **Ya**如果**是**,
Type of pet / Jenis haiwan宠物类型: _____

Pets are kept in the house, outside the house or both? Haiwan disimpan di dalam rumah, di luar rumah atau kedua-duanya?
宠物被养在屋内，屋外或两者都有？_____

3. Does your child attend daycare center (includes nursery, babysitter's house, kindergarden)? Adakah anak anda menghadiri pusat jagaan harian (termasuk taska, rumah pengasuh bayi, bilik permainan, tadika)? 您的孩子有参加日托中心吗(包括托儿所, 保姆的家, 幼儿园)？

a. Yes / Ya 是 (Age of first time attending daycare / Umur pertama kali menghadiri pusat jagaan harian第一次参加日托中心的年龄: _____)

b. No / Tidak 否

4. In the past 3 months, was your child given any antibiotics? Dalam tempoh 3 bulan yang lepas, adakah anak anda diberi sebarang antibiotik?
在过去的三个月中，您的孩子是否服用过任何抗生素？

a. Yes / Ya 是 b. No / Tidak 否

Part C：Eczema in infants / Bahagian C: Eczema pada bayi (C项：婴儿湿疹)

In the past 3 months / Dalam tempoh **3 bulan yang lepas**, 在**过去的3个月内**,		**Yes** **Ya**是	**No** **Tidak**否
1	Has your child had an itchy skin condition - itchy mean scratching or rubbing the skin a lot? Adakah anak anda mempunyai keadaan kulit gatal – gatal bermaksud menggaru atau menggosok kulit dengan kerap? 您的孩子有皮肤瘙痒的情况吗-瘙痒的意思是很常搔抓或摩擦皮肤？		Go to C3 Pergi ke C3 转到C3
2	Has this skin condition ever affected the skin creases of your child - skin creases mean fronts of elbows, behind the knees, fronts of ankles, around the neck, around eyes or cheeks? Adakah keadaan kulit ini pernah menjejaskan lipatan kulit anak anda – lipatan kulit bermaksud depan siku, belakang lutut, bahagian depan buku lali, di sekitar kawasan leher atau mata, pada pipi? 这种皮肤状况曾影响您孩子的皮肤皱褶处吗-皮肤皱褶处的意思是肘弯处, 膝关节后方 , 踝关节前方, 脸颊, 颈部或眼睛周围？		
3	Does anyone in your child's immediate family (i.e. mother, father, brothers or sisters) suffer from eczema, hay fever or asthma? Adakah sesiapa dalam ahli keluarga terdekat anak anda menghidapi ekzema, hay demam atau asma? 您孩子的直系亲属(母亲, 父亲, 兄弟姐妹)有患上湿疹, 花粉过敏或哮喘吗？		
4	Has your child suffered from a general dry skin? Adakah anak anda menghadapi masalah kulit kering secara umum? 您的孩子有遭受一般皮肤干燥的问题吗？		
Signs to be ascertained by researcher / Tanda-tanda untuk dipastikan oleh penyelidik 研究人员须确定的症状			
5	Is there visible fiexural dermatitis in the child (scaling, crusting, vesicles or Iichenification)? Adakah kanank-kanak tersebut mempunyai eczema lenturan yang boleh dilihat (kulit bersisik, mengelupas, vesikel, atau keras dan tebal)?		

	孩子有明显的屈部湿疹吗(皮肤脱屑, 脱皮, 生水疱, 或硬厚)? Have one or more patches of dermatitis affecting any of the following sites / Mempunyai satu atau lebih tompok dermatitis yang menjejaskan mana-mana bahagian berikut 拥有一处或多处影响下列部位的湿疹: - behind the knees / Belakang lutut膝关节后方 - fronts of ankles / Bahagian depan buku lali踝关节前方 - fronts of elbows / Depan siku肘弯处 - sides or front of the neck / Di sisi atau depan leher颈部侧面或正面 - around the ears or eyes / Di sekitar telinga atau mata耳朵或眼睛周围 - cheeks / Pipi脸颊		
6	Has your child ever had eczema? Pernahkah anak anda menghidapi ekzema? 您的孩子是否患有过湿疹?		
7	Was your child eczema been diagnosed by a doctor? Adakah ekzema anak anda telah didiagnosis oleh doktor? 您孩子的湿疹是否有被医生诊断过?		

Part D：Food allergy in infants / Bahagian D：Alergi makanan pada bayi (D项：婴儿食物过敏

1. In the **past 3 months**, has your child ever had rash in the skin and sickness within two hours of eating some food?
Dalam tempoh **3 bulan yang lepas**, adakah anak anda mempunyai ruam merah di kulit atau sakit dalam masa dua jam selepas makanan makanan tertentu?
在过去的3个月内， 您的孩子是否在吃了特定的食物后的2小时内出现红疹或症状?

a. Yes / Ya 是 (Please specify the symptoms / Sila nyatakan symptom 请说明症状: _____) b. No / Tidak 否

2. Were these symptoms repeating each time the same food was eaten? Adakah simptom-simptom ini berulang setiap kali makanan yang sama dimakan?
这些症状是否在每一次食用同样的食物时重复发生?

a. Yes / Ya 是 b. No / Tidak 否

3. If Yes, what food that your child allergy to? Jika **Ya**, makanan apakah yang anak anda alergi? 如果**是**，您的孩子对什么食物过敏?

a. Egg / Telur蛋
b. Tree nut (Almonds, hazelnuts, walnuts, cashews, chestnuts) / Kekacang (Badam, hazelnuts, walnuts, cashews, chestnuts) 木本坚果(杏仁, 榛子, 合桃, 腰果, 栗子)
c. Peanut / Kacang tanah花生
d. Milk / Susu牛奶
e. Shellfish (Oysters, mussels, shrimp, crab, squid) / Kekerang (Tiram, kupang, udang, ketam, sotong) 贝类(牡蛎, 贻贝, 虾, 螃蟹, 章鱼)
f. Fish / Ikan鱼
g. Wheat / Wheat小麦
h. Soybean / Kedelai黄豆
i. Others Lain-lain其他 (Please state / Sila nyatakan请说明: _____)

4. Have your child food allergy been diagnosed by a doctor? Adakah alergi makanan anak anda telah didiagnosis oleh doktor?
您孩子的食物过敏是否有被医生诊断过?

a. Yes / Ya 是 b. No / Tidak 否

If yes, please state the diagnostic method / Jika Ya, sila nyatakan cara diagnosis 如果**是**，请说明诊断方式:

a. Physical examination / Pemeriksaan fizikal身体检查
b. Ig E blood test / Ujian darah Ig E血液测试
c. Skin Prick Test / Ujian Cucuk Kulit皮肤点刺试验
d. Food Challenge Test / Uji Provokasi Makanan食物激发试验
e. Others Lain-lain**其他** (Please state / Sila nyatakan请说明: _____)

Part E：Infant feeding practices / Bahagian E: Amalan pemberian makanan bayi (E项：婴儿喂养方式)

1. Is your child ever being breastfed? Adakah anak anda pernah disusukan dengan susu ibu (susu badan)? 您的孩子曾被喂食母乳吗?

a. Yes / Ya是 b. No / Tidak否

2. Is your child still being breastfeed? Adakah anak anda masih disusukan dengan susu ibu (susu badan)? 您的孩子还在被喂食母乳吗?

a. Yes b. No/ Tidak否

3. At what age did your child stopped the breastfeed? Berapakah umur anak anda semasa berhenti menyusu susu ibu (susu badan)?
当您的孩子被停止喂食母乳时是多少岁?

_____ days / hari天
_____ weeks / minggu个星期

4. In the last 24 hours (during the day and night), was your child given any drinks or foods using feeding bottle with teat including expressed breast milk?
Dalam tempoh **24 jam yang lepas** (siang dan malam), adakah anak anda diberi apa-apa minuman atau makanan menggunakan **botol susu dengan puting** termasuk susu ibu di dalam botol? 在过去的**24小时内**(白天和夜晚)，您有使用**有奶嘴的奶瓶**喂食您的孩子任何饮料或食物包括母乳吗?

a. Yes / Ya是 b. No / Tidak否

5. Was your child given any vitamin drops or other medicines as drops in the last 24 hours (during the day and night)?
Adakah anak anda diberi apa-apa titisan vitamin atau titisan ubat-ubatan lain dalam tempoh **24 jam yang lepas** (siang dan malam)?
在过去的**24小时内**(白天和夜晚)，您的孩子有被喂食任何维生素滴剂或其他药物吗?

a. Yes / Ya是 b. No / Tidak否

6. In the last 24 hours (during the day and night) was your child given the following liquids including liquids consumed outside home?
Dalam tempoh 24 jam yang lepas (siang dan malam), adakah anak anda diberi miuman berikut termasuk minuman yang diambil di luar rumah?
在过去的24小时内(白天和夜晚), 您的宝宝有被喂食以下饮料包括在家之外喂食的饮料吗?

	Liquids / Minuman饮料	**Yes Ya是**	**No Tidak否**
a	Plain water / boiled water / mineral water / Air kosong/ air masak/ air mineral清水/开水/矿泉水		
b	Fresh fruit juice / Jus segar daripada buah新鲜果汁		
c	Sugared water (commercial fruit juices, cordial, syrup, tea, malted drinks for example milo, vico, ovaltine, horlick) Minuman bergula (seperti minuman jus buah komersial, kordial, air sirap, teh/ minuman bermalta contohnya milo, vico, ovaltine, horlick)? 含糖饮料 (例如商业果汁，糖浆，茶/麦芽饮料)		
d	Oral Rehydration Salt (ORS) – **With** health personal's prescription (doctor/medical assistant) / Air garam/ ORS – Dengan preskripsi anggota kesihatan (Doktor/Penolong Pegawai Perubatan) 盐水-有医务人员开的处方(医生/医务人员助理)		
e	Oral Rehydration Salt (ORS) – **Without** health personal's prescription (doctor/medical assistant) / Air garam/ ORS – **Tanpa** preskripsi anggota kesihatan (Doktor/Penolong Pegawai Perubatan) 盐水-没有医务人员开的处方(医生/医务人员助理)		
f	Vitamin or mineral supplement or any medicines – **With** health personal's prescription (doctor/medical assistant) / Vitamin atau mineral tambahan atau sebarang ubat-ubatan – **Dengan** preskripsi anggota kesihatan (Doktor/Penolong Pegawai Perubatan) 维生素或矿物质补充剂或任何药物 -有医务人员开的处方(医生/医务人员助理)		
g	Vitamin or mineral supplement or any medicines – **Without** health personal's prescription (doctor/medical assistant) / Vitamin atau mineral tambahan atau sebarang ubat-ubatan – **Tanpa** preskripsi anggota kesihatan (Doktor/Penolong Pegawai Perubatan) 维生素或矿物质补充剂或任何药物 -没有医务人员开的处方(医生/医务人员助理)		
h	Clear soup (chicken, fish, meat, vegetable soup) / Kuah sup (seperti air rebusan ayam, ikan, daging, sayur) 清汤(例如鸡汤，鱼汤, 肉汤, 蔬菜汤)		
i	Infant formula / Susu formula bayi婴儿配方奶粉 (**Brand /Jenama 牌子:** _____)		
j	Milk other than breastmilk and infant formula such as powdered, or fresh animal milk / Susu selain susu ibu dan susu formula bayi (susu tin, susu tepung atau susu segar daripada sumber haiwan contohnya susu kambing/susu lembu segar) 除了母乳和婴儿配方奶粉以外的牛奶(罐装牛奶，奶粉或鲜奶例如鲜羊奶/牛奶)		
k	Thin porridge / Bubur 稀粥		
l	Other liquids / Minuman lain其他饮料 (Please state / Sila nyatakan请说明: _____)		

7. In the last 24 hours (during the day and night), was your child given the following food including food consumed outside home?
Dalam tempoh 24 jam yang lepas (siang dan malam), adakah anak anda diberi makanan berikut termasuk makanan yang diambil di luar rumah.
在过去的24小时内(白天和夜晚),您的宝宝有被喂食以下食物包括在家之外喂食的食物吗?

	Food / Makanan食物	**Yes Ya是**	**No Tidak否**
a	Other food made from milk (such as buttermilk, yogurt, cheese, butter) Hasil ternusu (seperti dadih, yogurt, keju, mentega) 奶制食品(如酪乳, 酸奶,奶酪,黄油)		
b	Commercial baby foods (such as cereal based infant foods) / Makanan khas untuk bayi yang dikomersialkan (contohnya makanan bayi berasaskan bijirin) 商业婴儿食品(如婴儿谷类食品)		
c	Cereal based foods (such as rice, bread, noddles) / Makanan berasaskan bijirin (seperti nasi, roti, mee, bubur) 谷类食品(例如饭，面包，面条)		
d	Pumpkin, carrot, and yellow or orange sweet potatoes Labu manis, lobak merah, keledek yang berwarna kuning atau oren黄或橙色的南瓜，红萝卜，番薯		
e	White potatoes, white yams, tapioca, or any other food made from roots / Ubi-ubian yang berwarna putih (seperti ubi kentang, ubi keladi putih, keladi Sarawak, ubi kayu) 白薯类(例如土豆，芋头，木薯)		
f	Any green leafy vegetables / Sebarang sayuran berdaun hijau 任何绿叶蔬菜		
g	Fruits rich in vitamin A such as ripe, mango, papaya, banana, waterrmelon, rock melon / Buah-buahan yang kaya kandungan vitamin A seperti mangga, betik, tembikai, pisang, tembikai susu, rock melon含有丰富维生素A的水果如芒果，木瓜, 西瓜, 香蕉, 蜜瓜		
h	Other fruits and vegetables (such as rambutan, starfruit, tomato, cabbage, cauliflower and corn) / Buah-buahan dan sayuran lain (seperti rambutan, belimbing, tomato, kobis, bunga kobis dan jagung其他水果和蔬菜（如红毛丹, 杨桃, 番茄, 白菜, 花椰菜和玉米）		
i	Liver or other animal's internal organ / Hati atau organ dalaman haiwan肝脏或动物内脏		
j	Any meat (such as chicken, duck, beef, lamb, pork) / Sebarang daging (seperti ayam, itik, lembu, kambing, khinzir) 任何肉类(例如鸡，鸭，牛，羊，猪)		
k	Eggs (such as chicken, duck, quail, goose) / Telur (seperti ayam, itik, puyuh, angsa) 蛋(例如鸡，鸭，鹌鹑，鹅)		
l	Fresh fish, dried fish, anchovies or seafoods (such as squid, shrimp) / Ikan segar, ikan kering atau makanan laut (seperti sotong, udang, ikan bilis) 鲜鱼，鱼干或海鲜（例如鱿鱼，虾，江鱼仔）		
m	Any food made from beans, lentils or nuts (such as green bean, peas and peanut) / Makanan berasaskan kacang dan kekacang (seperti kacang hijau, kacang pis, kacang dhal dan lain-lain kekacang) 任何豆类食物(例如青豆，豌豆, 花生)		
n	Any oil, fats, or butter, or foods made with any of these / Minyak, lemak, mentega, atau makanan yang diperbuat daripada bahan ini 任何油，脂肪，牛油，或相关材料制成的食品		
o	Any sugary foods such as chocolates, sweets, candies, pastries, cakes, or biscuits / Makanan manis seperti coklat, gula-gula, pastri, kek, atau biskut含糖食物，如巧克力，糖果，糕点，蛋糕，或饼干		
p	Condiments for flavor, such as chilies, spices or herbs / Perasa seperti cili, rempah, atau herba 调味品如辣椒, 香料或药材		
q	Solid, semi-solid, or soft foods / Makanan pepejal, separa pepejal atau lembut 其他固体，半固体食物或软食 (Please state / Sila nyatakan 请说明: _____)		

Appendices

Appendix 11: Published Article (Woon et al., 2019)

PLOS ONE

RESEARCH ARTICLE

Vitamin D deficiency during pregnancy and its associated factors among third trimester Malaysian pregnant women

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Abstract

Background

Despite perennial sunshine, vitamin D deficiency is prevalent among Malaysians especially pregnant women. This study determines the vitamin D status and its associated factors among third trimester pregnant women attending government health clinics in Selangor and Kuala Lumpur, Malaysia.

Methods

Information on socio-demographic characteristics, obstetrical history, and sun exposure were obtained through face-to-face interviews. Vitamin D intake was assessed using a semi-quantitative food frequency questionnaire (FFQ). Serum 25-hydroxyvitamin D concentration was measured and classified as deficient (< 30 nmol/L), insufficient (30–50 nmol/L), and sufficient (≥ 50 nmol/L).

Results

Of the 535 pregnant women recruited, 42.6% were vitamin D deficient. They consumed an average of 8.7 ± 6.7 μg of vitamin D daily. A total of 80.4% of the vitamin D were obtained from the food sources, while 19.6% were from dietary supplements. Fish and fish products showed the highest contribution to vitamin D intake (35.8%). The multivariable generalized linear mixed models, with clinic as a random effect, indicates that higher intake of vitamin D is associated with lower odds of vitamin D deficiency among pregnant women (OR = 0.96; 95% CI = 0.93–0.99). The odds of having vitamin D deficiency was reduced by 87% in non-Malays (OR = 0.14; 95% CI = 0.05–0.41) compared to Malays. No associations were found

Competing interests: The authors have declared that no competing interests exist.

between age, educational level, monthly household income, work status, gravidity, parity, pre-pregnancy body mass index, total hours of sun exposure, total percentage of body surface area, and sun exposure index per day with vitamin D deficiency.

Conclusion

Vitamin D deficiency is prevalent among Malaysian pregnant women. Considering the possible adverse obstetric and fetal outcomes of vitamin D deficiency during pregnancy, future nutrition education should emphasise on vitamin D-fortified foods consumption among pregnant women by taking into consideration ethnic differences.

Introduction

Vitamin D, an essential fat-soluble vitamin or steroid prohormone, plays an important role in the regulation of calcium and phosphorus homeostasis and bone mineralization [1]. There are three main sources of vitamin D which include sunlight exposure, dietary sources, and supplement intake. Sunlight exposure is the primary source of vitamin D in the tropical countries and is mainly influenced by environmental and personal factors such as seasons, geographic latitude, skin type, the percentage of body surface exposed to sunlight, and clothing [2,3]. Once ingested or produced by the body through skin exposure to the ultraviolet B radiation from the sun, both vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) are transported to the liver and is hydroxylated to 25-hydroxyvitamin D (25(OH)D) [4]. 25(OH)D is the major circulating form of vitamin D in human body [5]. Serum 25(OH)D is widely recognized as the best biochemical indicator of vitamin D status as it reflects the cumulative exposure to sunlight and dietary vitamin D intake of an individual [6]. Identifying the level of circulating 25(OH)D is important for diagnosis and monitoring of vitamin D deficiency [6].

Though there is no consensus on optimal 25(OH)D levels, vitamin D deficiency has been identified as a global health problem and has affected more than 1 billion people globally [7,8], especially among pregnant women. The prevalence of vitamin D deficiency and insufficiency during pregnancy ranges from 27.0% to 91.0% in the United States, 39.0% to 65.0% in Canada, 45.0% to 100.0% in Asia, 19.0% to 96.0% in Europe, and 25.0% to 87.0% in Australia and New Zealand [8]. Despite being a tropical country with perennial sunshine, vitamin D deficiency in pregnant women has been reported in Malaysia. A recent study conducted at a tertiary hospital in Kuala Lumpur found that 71.7% of the third trimester pregnant women had vitamin D deficiency and 21.0% had vitamin D insufficiency [9]. Another local study reported 90.4% of the first trimester pregnant women in the Klang Valley had vitamin D insufficiency and deficiency [10]. A cohort study in Kelantan, Malaysia found that 59.8% and 37.3% of pregnant women had vitamin D deficiency during their second and third trimesters, respectively [11].

Low maternal vitamin D levels during pregnancy have been linked with multiple adverse obstetric outcomes such as maternal osteomalacia [12], gestational diabetes [13], preeclampsia [14], and primary cesarean section [15]. In addition, gestational vitamin D deficiency is associated with fetal intrauterine growth restriction and various adverse fetal and neonatal health outcomes, including higher risk of premature birth [16], abortion [17], low birth weight [18], neonatal hypocalcaemia [19], and childhood obesity [20].

Given the high prevalence of vitamin D deficiency among pregnant women and its adverse pregnancy outcomes, there is an urgent need to determine factors contributing to vitamin D deficiency during pregnancy in order to design effective prevention strategies that might

reverse these alarming trends. Therefore, the aim of this study was to determine the prevalence of vitamin D deficiency among pregnant women in Selangor and Kuala Lumpur and to identify potential factors associated with vitamin D deficiency during the third trimester of pregnancy.

Materials and methods

Study design and respondents

This study is part of the Mother and Infant Cohort Study (MICOS) and the protocol of the study was previously described [21]. This study was conducted at six selected government Maternal and Child Health clinics in the state of Selangor (3.074˚ N) and the city of Kuala Lumpur (3.139˚ N), Malaysia. Written informed consent was obtained from the respondents prior to data collection. Between November 2016 and January 2018, Malaysian women aged 18 years and above with singleton pregnancies of more than 28 weeks of gestations were invited to participate in the study during their routine prenatal check-ups at the selected clinics. Women with multiple pregnancies and planned to move out of the study area in the next one year were excluded from the study. Out of 3982 pregnant women who were invited to participate, 535 women consented and completed the study.

Maternal vitamin D status

Vitamin D status was determined based on serum 25(OH)D analysis. A venous blood sample (2ml) was collected from the respondents. The serum samples were sent to the laboratory and analysed using the Siemens ADVIA Centaur Vitamin D Total assay (Siemens, Tarrytown, NY, USA). This assay has been standardized to the University of Ghent ID-LC/MS/MS reference measurement procedure [22] and has achieved the Centers for Disease Control Vitamin D Standardization Certification [23]. Serum 25(OH)D level was classified into vitamin D deficiency (< 30 nmol/L), vitamin D insufficiency (30–50 nmol/L) and vitamin D sufficient (≥ 50 nmol/L) [24].

Maternal characteristics

Socio-demographic data including age, ethnicity, educational level, working status, monthly household income, and obstetrical history such as parity and gravidity were obtained from the respondents through a face-to-face interview. Pre-pregnancy body weight and height were obtained from medical records. Pre-pregnancy Body Mass Index (BMI) was calculated and classified based on World Health Organization (WHO) cut-off points [25].

Maternal vitamin D intake and supplementation

Vitamin D intake and supplementation were assessed using a Vitamin D Food Frequency Questionnaire (FFQ) over the past month [26]. The vitamin D FFQ consists of foods derived from three categories; namely, foods that naturally contained vitamin D, foods that were fortified with vitamin D, and supplements that contained vitamin D. As vitamin D content is not available in Malaysian food composition table, the vitamin D content of raw food was obtained from the United States Department of Agriculture National Nutrient Database for Standard Reference [27] and Food Composition System Singapore. Meanwhile, vitamin D content of the fortified commercial products including milk and milk products, canned fish, bread spread, beverages, cereal and cereal products, and supplements were obtained from the products' label. In Malaysia, foods claiming to be fortified with vitamin D must be at least 5% of the Nutrient Reference Value (NRV) per serving in order to be declared on a food label [28]. The

daily average vitamin D intake (μg/day) was calculated by multiplying the frequency of consumption per day, serving size consumed, and vitamin D content of the food. The vitamin D intake was then compared with the Recommended Nutrient Intakes (RNI) for Malaysians [29] to determine the nutrient intake adequacy. The percentage contribution of each food group to total vitamin D intake was calculated to determine the main food sources of vitamin D.

Maternal sun exposure

Sun exposure was assessed by using a Seven-day Sun Exposure Recall [30]. Respondents were required to record their outdoor activities over the past one week (from 7am to 7pm) in terms of type of activity, duration (in minutes), frequency (per week), clothing, sunscreen use, gloves, and umbrellas. Body surface area (BSA) exposed to sunlight was estimated by using the "Rule of Nine" adopted from Hall et al. [30]. Sun exposure index (SEI) was calculated by multiplying the amount of time spent outdoors with BSA exposed.

Data analysis

The IBM SPSS Statistics 24 software (SPSS Inc., Chicago, IL, USA) was used to analyse the data. Descriptive statistics such as mean and standard deviation (SD), as well as frequency and percentage were performed. Generalized linear mixed models (GLMM) were used to examine the associations between socio-demographic factors (gestation age, ethnicity, educational level, working status, monthly household income), obstetrical factors (gravidity, parity, pre-pregnancy BMI), and behavioral factors (vitamin D intake, intake of supplements contain vitamin D, total hours of sun exposure per day, total percentage of BSA per day, total SEI per day) with vitamin D deficiency during pregnancy. First, a model was fitted with only clinic entered as a random effect to determine the within-clinic intra-class correlation coefficient. Second, socio-demographic, obstetrical, and behavioral factors were individually added as fixed effects in the model adjusted for clinic clustering. Variables that were significant at the $p < 0.2$ level were retained for the final model. Third, an adjusted final model was fitted with the socio-demographic, obstetrical, and behavioral factors that were found to be significantly associated with vitamin D deficiency, and associations among these variables were assessed while controlling for clinic clustering. Data were presented as odd ratios (OR) with 95% confidence interval (CI). The statistical significance was set at $p < 0.05$.

Ethics statement

Ethical approvals for the study were obtained from the Ethics Committee for Research Involving Human Subjects, Universiti Putra Malaysia [FPSK(FR16)P006] and the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-16-1047-30685).

Results

Vitamin D status of the respondents

The mean serum 25(OH)D concentration for the total 535 pregnant women was 33.8 nmol/L (SD = 12.9) (Table 1). Based on the Institute of Medicine (IOM) classification [24], the prevalence of vitamin D deficiency (< 30 nmol/L), vitamin D insufficiency (30–50 nmol/L), and normal vitamin D (≥ 50 nmol/L) was 42.6%, 49.3%, and 8.0%, respectively.

Characteristics of the respondents

The mean age at conception of the respondents was 29.9 (SD = 4.1) years (Table 2). Majority of them were Malay (92.1%), attained a tertiary education (81.7%), and had a moderate

Table 1. Vitamin D status of the respondents (n = 535).

25(OH)D (nmol/L)	n	%
Mean (SD)	33.8 (12.9)	
Deficient (< 30 nmol/L)	228	42.6
Insufficient (30–50 nmol/L)	264	49.4
Sufficient (≥ 50 nmol/L)	43	8.0

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household income (52.3%). Most of them were employed (69.0%), multigravida (65.2%), and nulliparous (42.1%). In relation to pre-pregnancy BMI, the prevalence of underweight, overweight, and obesity was 9.0%, 25.0%, and 11.8%, respectively. The respondents consumed an average of 8.7 ± 6.7 μg of vitamin D daily, with three-quarters of them did not achieve the RNI for vitamin D which is 15 μg/day (74.4%). Overall, the median SEI of the respondents was 0.57. The median percentage of BSA of the respondents was 1.14% by taking into account of the face, neck, arms, hands, legs, and feet being exposed to the sunlight, as well as the clothing

Table 2. Characteristics of the respondents (n = 535).

Characteristics		n	%
Age at conception (years)	Mean (SD)	29.9 (4.1)	
Ethnicity	Malay	439	92.1
	Non-Malay	42	7.9
Educational level	Secondary	98	18.3
	Tertiary	437	81.7
Monthly household income[a]	Low (< RM2300)	93	17.4
	Moderate (RM2300-RM5599)	280	52.3
	High (> RM5600)	162	30.3
Work status	Non-working	166	31.0
	Working	369	69.0
Gravidity	Primigravida	186	34.8
	Multigravida	349	65.2
Parity	Nulliparous	225	42.1
	Primiparous	139	26.0
	Multiparous	171	32.0
Pre-pregnancy BMI (kg/m^2)	Mean (SD)	24.1 (4.9)	
	Underweight (< 18.5 kg/m^2)	48	9.0
	Normal weight (18.5–24.9 kg/m^2)	290	54.0
	Overweight (25.0–29.9 kg/m^2)	134	25.0
	Obesity (≥ 30.0 kg/m^2)	63	11.8
Dietary vitamin D intake (μg/day)	Mean (SD)	10.2 (7.9)	
	Below RNI (< 15 μg/day)	398	74.4
	Above RNI (≥15 μg/day)	137	25.6
Intake of supplements containing vitamin D	No	355	66.4
	Yes	180	33.6
Total minutes of sun exposure per day	Median (IQR)	4.29 (0.00, 17.14)	
Total % BSA per day	Median (IQR)	1.14 (0.00, 5.14)	
SEI per day	Median (IQR)	0.57 (0.00, 0.57)	

BSA, Body Surface Area; IQR, Interquartile Range; RM, Ringgit Malaysia; RNI, Recommended Nutrient Intakes; SEI, Sun Exposure Index

[a]1 US dollar = RM 4.09 (as of March 16, 2019)

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Table 3. Contribution of food items towards the daily mean intake of vitamin D among the respondents.

Food item	Contribution (%)
Fish and fish products	35.87
Indian mackerel	13.78
Eastern little tuna	8.90
Prawn	4.59
Spanish mackerel	4.51
Salmon	2.11
Anchovy	0.98
Canned sardine	0.93
Canned tuna	0.05
Canned mackerel	0.02
Milk and milk products	28.19
Fresh milk (Full cream/Low-fat/Flavored)	19.31
Maternal milk powder	4.82
Milk powder (Full cream/Low-fat)	2.71
Sweetened condensed milk	0.49
Cheese	0.41
Ice-cream	0.25
Butter	0.20
Eggs	9.13
Meat and meat products	3.85
Chicken	3.54
Beef	0.20
Beef sausage	0.05
Pork	0.04
Cow liver	0.02
Others	1.31
Margarine	0.88
Mushroom	0.38
Mashed potatoes	0.05
Beverages	1.22
Cultured milk drinks	1.21
Fortified soy drinks	0.01
Cereal and cereal products	0.86
Cereal drinks	0.83
Pancake	0.02
Waffle	0.01
Supplements containing vitamin D	19.57

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and the usage of sunscreen. The respondents spent about of 4.29 minutes per day being exposed to the sunlight.

A total of 80.4% of the vitamin D were obtained from the food sources, while the rest were from dietary supplements (19.6%) (Table 3). Only one in three of the respondents took supplements containing vitamin D during pregnancy (33.6%). Fish and fish products (35.8%) showed the highest contribution to vitamin D intake, followed by milk and milk products (28.2%), eggs (9.1%), meat and meat products (3.9%), others (1.3%), beverages (1.2%), and cereal and cereal products (0.9%).

Table 4. Factors associated with maternal vitamin D deficiency [25(OH)D <30 nmol/L].

Variables	Model 1		Model 2	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age at conception (years)	0.97 (0.93, 1.01)	0.158	0.98 (0.94, 1.03)	0.481
Ethnicity			-	
Non-Malay	0.13 (0.04, 0.36)	< 0.001	0.14 (0.05, 0.41)	< 0.001
Malay	1		1	
Educational level			-	
Secondary	1.17 (0.75, 1.83)	0.476	-	
Tertiary	1		-	
Monthly household income (RM)			-	
Low (< RM2300)	1.24 (0.77, 1.98)	0.377	1.09 (0.67, 1.77)	0.739
Moderate (RM2300-RM5599)	1		-	
High (> RM5600)	0.73 (0.49, 1.08)	0.115	0.86 (0.56, 1.32)	0.492
Work status			-	
Non-working	0.91 (0.62, 1.31)	0.598	-	
Working	1		-	
Gravidity			-	
Primigravida	1.04 (0.72, 1.49)	0.849	-	
Multigravida	1		-	
Parity			-	
Nulliparous	1		-	
Primiparous	1.01 (0.66, 1.55)	0.963	-	
Multiparous	0.98 (0.65, 1.46)	0.905	-	
Pre-pregnancy BMI (kg/m2)			-	
Underweight (< 18.5)	0.80 (0.43, 1.51)	0.494	-	
Normal weight (18.5–24.9)	1		-	
Overweight/obesity(≥ 25.0)	1.04 (0.72, 1.50)	0.827	-	
Intake of supplements containing vitamin D				
No	1		1	
Yes	0.52 (0.36, 0.75)	0.001	0.99 (0.59, 1.59)	0.899
Vitamin D intake (μg/day)	0.96 (0.93, 0.98)	< 0.001	0.96 (0.93, 0.99)	0.006
Total hours of sun exposure per day	1.06 (0.66, 1.70)	0.809	-	
Total % BSA per day	0.98 (0.96, 1.00)	0.109	0.99 (0.97, 1.02)	0.586
SEI per day	1.06 (0.66, 1.70)	0.809	-	

BSA, Body Surface Area; CI, Confidence Interval; OR, Odds Ratio; SEI, Sun Exposure Index

Factors associated with maternal vitamin D deficiency [serum 25(OH)D < 30nmol/L] were estimated using generalized linear mixed models adjusted for clinic clustering. In the null model (Model 1), the ICC was 0.01 (95% CI = 0.00, 1.50) with clinic as a random effect. Only variables that were significantly associated with vitamin D deficiency in the bivariable models (Model 2) were included in the multivariable model (Model 3).

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Factors associated with maternal vitamin D deficiency

As shown in Table 4, the estimated intercept and 95% CI in the null model was 0.01 (95% CI = 0.00, 1.50). In the bivariable model adjusted for clinic clustering (Model 1), non-Malay (OR = 0.13, 95% CI = 0.04, 0.37), intake of supplements containing vitamin D (OR = 0.52, 95% CI = 0.36, 0.75), and higher dietary vitamin D intake (OR = 0.96, 95% CI = 0.93, 0.98) were significantly associated with lower odds of having vitamin D deficiency compared to their counterparts. No associations were found between age, educational level, monthly

household income, work status, gravidity, parity, pre-pregnancy BMI, total hours of sun exposure, total percentage of BSA, and SEI per day with vitamin D deficiency.

In the multivariable model adjusted for clinic clustering (Model 2), ethnicity and dietary vitamin D intake remained significant. The odds of having vitamin D deficiency was reduced by 87% in non-Malays (OR = 0.13, 95% CI = 0.04, 0.37). Meanwhile, pregnant women who had higher intake of vitamin D were less likely to have vitamin D deficiency during pregnancy (OR = 0.96, 95% CI = 0.93, 0.99). The association between intake of supplements containing vitamin D with vitamin D deficiency was no longer significant.

Discussion

The present study revealed that 42.6% of the pregnant women were vitamin D deficient and almost half were vitamin D insufficient (49.3%). Women who had higher intake of dietary vitamin D and being non-Malays were less likely to have vitamin D deficiency during pregnancy.

High prevalence of vitamin D deficiency and insufficiency have been reported in several studies in the tropical countries [31–33]. A recent study conducted in West Sumatra, Indonesia reported the prevalence of vitamin D deficiency and insufficiency among third trimester pregnant women was 61.3% [31]. Another study found that 60.0% of Vietnamese women at 32 weeks gestation had low vitamin D levels [32]. In Thailand, 75.5% of the pregnant women had hypovitaminosis at the time of giving birth [33]. The prevalence of vitamin D deficiency and insufficiency in the present study was much higher than those reported in the aforementioned studies which used different serum 25(OH)D cut-off level of < 75 nmol/L. To date, there is still lack of consensus on the definition of vitamin D levels. While IOM defined a serum 25 (OH)D level less than 30 nmol/L as deficiency and 30–50 nmol/L as insufficiency [24], the Endocrine Society Task Force set a higher cut-off values for vitamin D deficiency [25(OH) D < 50 nmol/L] and insufficiency [25(OH)D 50–74 nmol/L] [34]. The IOM definitions were used in this study as findings from previous studies indicated that a deficient serum 25(OH)D level below 30 nmol/L was associated with increased risk of adverse skeletal health outcomes including osteomalacia [24]. Meanwhile, insufficient serum 25(OH)D level of 30–50 nmol/L could lead to hyperparathyroidism, accelerated bone turnover and osteoporosis [24].

In this study, pregnant women who had higher intake vitamin D were more likely to have lower odds of vitamin D deficiency. This finding is in agreement with Shiraishi et al. [35] that found higher vitamin D intake significantly contributed to higher serum 25(OH)D concentration among pregnant women. This could be attributed to the high consumption of vitamin D containing food. Similarly, a recent local study conducted by Yong et al. [36] demonstrated that milk and dairy products were the major food sources contributing to vitamin D intake among pregnant women.

In the current study, we found that among third trimester pregnant women, those who were Malays were at a higher risk for vitamin D deficiency as compared to the non-Malays. The significant ethnic differences in the prevalence of vitamin D deficiency was in line with previous studies conducted among general population and pregnant women in Malaysia, showing that Malays had the highest prevalence of vitamin D deficiency than non-Malays [19,37]. The high prevalence of vitamin D deficiency might be due to religious and cultural reasons. Muslim women are compulsory to cover entire body parts [38] and this reduces the probability for the Malay pregnant women to get sufficient sunlight, which will then lower the vitamin D production in their body. Similarly, previous studies conducted in Islamic countries such as Iran and Pakistan reported high prevalence of vitamin D insufficiency and deficiency among Muslim pregnant women [39,40]. Besides, our study found that Malay pregnant women spent lesser time outdoor and had a lower body surface area exposed to the sunlight as

compared to the non-Malays, which indirectly contributes to lower vitamin D production in the body.

Only one in three women in the study were taking dietary supplements containing vitamin D, such as multivitamins and calcium supplements enriched with vitamin D. Intake of supplements containing vitamin D significantly lowered the risk of vitamin D deficiency in the bivariable model but was no longer significant in the multivariable model. This finding was inconsistent with previous studies conducted among pregnant Japanese [35] and Chinese [41] women, in which the use of vitamin D supplements and multivitamins were associated with higher serum 25(OH)D levels. One of the possible explanations for these findings is that the use of vitamin D supplements was uncommon among Malaysian pregnant women. We also found that the major contributor of vitamin D was from food sources, while dietary supplements only contributed towards less than a quarter of the total vitamin D intake.

In line with the findings reported in a local study conducted among pregnant women in an urban district in Malaysia [10], no association was found between sun exposure and vitamin D levels in this study. This might be due to low sun exposure in this population whereby they only spent about 30 minutes in a week being exposed to the sunlight. Similarly, a local study reported that pregnant women spent about 37 minutes a week exposed to the sunlight [10].

This study has several limitations. First, the cause-effect relationships between factors and vitamin D deficiency cannot be determined from the cross-sectional study design. Second, self-reported data on sun exposure and dietary vitamin D intake may lead to recall bias. High proportion of the invitees declined to participate in the study which resulted in low response rate of 13.4%. This may lead to selection bias which affects the external validity of the study. In addition, maternal vitamin D status was assessed only during the third trimester of pregnancy and the changes of vitamin D status during early pregnancy were unknown. These limitations may affect the generalisability of the study to other population. We acknowledge that other potential factors which may contribute to vitamin D levels, such as skin type, physical activity, season, or genetic background, were not examined in the present study and warrant further studies.

Conclusions

Although Malaysia is a country with abundant sunshine all year round, vitamin D deficiency was highly prevalent among third trimester pregnant women. High intake of vitamin D was found to be a protective factor for vitamin D deficiency, while Malay women had a higher risk of vitamin D deficiency. Future interventions for the prevention and control of maternal vitamin D deficiency should take into account of the ethnic differences. Considering the long term health complications of vitamin D deficiency during pregnancy, future nutrition education should emphasise on vitamin D-fortified foods consumption among pregnant women.

Supporting information

S1 Dataset. Dataset for study on vitamin D deficiency during pregnancy and its associated factors among third trimester Malaysian pregnant women (n = 535).
(XLSX)

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Appendices

Appendix 12: Published Article (Woon et al., 2020)

nutrients

MDPI

Article

Maternal Vitamin D Levels during Late Pregnancy and Risk of Allergic Diseases and Sensitization during the First Year of Life—A Birth Cohort Study

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Abstract: Allergic diseases are the most common chronic illness in childhood. Findings from developed countries have reported associations between Vitamin D levels during pregnancy and offspring allergy risk. This prospective cohort study aimed to determine the associations between maternal Vitamin D levels during late pregnancy and allergic diseases in Malaysian infants during the first year of life. Serum 25(OH)D concentrations of 380 pregnant women in the third trimester were measured using a chemiluminescent immunoassay. Children's allergic outcomes were assessed at 3, 6, and 12 months based on parental reports. Specific IgE antibodies against food and inhalant allergens were measured in infants at 12 months of age. A total of 43.2% pregnant women were Vitamin D deficient (<30 nmol/L) and 56.8% were nondeficient (≥30 nmol/L). A total of 27.6% of the infants had eczema, 6.1% had wheeze, 27.4% had food sensitization, 10.8% had inhalant allergen sensitization, and 3.8% had IgE-mediated food allergy during the first year of life. Compared with the nondeficient group, maternal Vitamin D deficiency in late pregnancy was not associated with any allergic outcomes after adjustment for potential confounding factors. In conclusion, the present study does not support an association between maternal Vitamin D levels in late pregnancy and allergic outcomes during the first year of life.

Keywords: 25-hydroxyVitamin D; pregnancy; allergic diseases; sensitization; infant

1. Introduction

Allergic diseases are the most common chronic illnesses in childhood and about 60% of allergies appear during first year of life [1]. Eczema and food allergy usually co-exist in early life, and eczema was proposed as an "entry point" for subsequent allergic diseases such as asthma and allergic rhinitis [1]. The global prevalence of allergic diseases has increased dramatically in recent decades and have

affected about 20% of the world's population [2]. The prevalence of allergic diseases including eczema, wheeze, and asthma, which were previously on the rise, have reached a plateau, or even started to decrease in some developed countries [3–5]. Conversely, emerging evidence shows that allergic disease prevalence, which was previously low, in developing countries continues to rise [6]. Development of eczema and food allergy early in life tends to increase the likelihood of developing other atopic diseases including asthma and allergic rhinitis in later childhood [1]. Apart from impaired quality of life, allergic diseases also place a profound social and financial burden on patients, their families, and society [2]. It is therefore important to identify the potentially modifiable risk factors of allergic diseases, so that early preventive measures can be taken.

The development of allergic diseases can be explained through the complex interplay between genetic inheritance and environmental exposures [2]. Although part of the increasing prevalence of allergic diseases in childhood can be explained by genetic predisposition, increased attention has been focused on the role of early life nutrition during the first 1000 days of life [7]. As diet is a modifiable risk factor, targeting the role of early life nutrition in the development of allergic diseases in children is essential for identifying potential primary prevention strategies. Vitamin D deficiency is one of the common micronutrient deficiencies during pregnancy [8]. Vitamin D, which has long been recognized for its importance in musculoskeletal health, has gained increased attention in recent years for its role in nonskeletal outcomes such as allergic diseases [9]. Findings from several birth cohorts suggested that maternal Vitamin D levels might play a role in the development of childhood allergic diseases [10–12]. During pregnancy, the fetus is totally dependent on the mother for an adequate supply of Vitamin D. Vitamin D in the fetus acquired from its mother through the placenta can affect immune development and subsequent risk of childhood allergy [13]. While findings from two birth cohorts revealed that a high maternal Vitamin D level is protective against childhood eczema, food allergy, and wheezing [10,12], others have shown that it is a risk factor for eczema and food allergy [11,14] or found no association [15]. Contradictory to the findings found in cohort studies, recent randomized controlled trials (RCTs) of Vitamin D supplementation in pregnancy have not proven to be effective against childhood allergies including eczema, food sensitization, wheeze, and asthma [16–20]. Results from previous studies have been controversial and most of these studies were conducted in developed countries. Therefore, more studies are needed to determine the role of Vitamin D levels during pregnancy in allergic diseases, especially in developing countries.

Despite the abundance of sunlight in Malaysia, a tropical country located right next to the equator, a high prevalence of Vitamin D deficiency has been reported among Malaysian pregnant women [21]. Considering the potential associations between maternal Vitamin D levels and allergy risk in children as reported in previous studies, Malaysian infants born to mothers with low Vitamin D levels during pregnancy might be at risk of allergy development. In view of the scarcity of prevalence data for childhood allergic diseases in Malaysia and that currently no study has examined their associations with maternal Vitamin D levels in this country, this study aims to determine the associations between maternal Vitamin D levels and the development of allergic diseases in infants during the first year of life.

2. Materials and Methods

2.1. Study Design and Study Population

This is a prospective cohort study conducted among pregnant women in late pregnancy participating in the Mother and Infant Cohort Study (MICOS) [22]. The protocol of the study and sample size calculation was previously described [22]. Between November 2016 and January 2018, the original cohort of 557 pregnant women was recruited at government Maternal and Child Health (MCH) clinics located in the state of Selangor and the Federal Territory of Kuala Lumpur, Malaysia. Participating pregnant women and their children were then followed up prospectively at 3, 6, and 12 months postpartum. The inclusion criteria were ≥18 years of age, gestation age ≥ 28 weeks at time

of recruitment, singleton pregnancy, and receiving antenatal care at the selected clinics. The exclusion criteria were multiple pregnancies, delivery before 37 weeks of gestation, maternal immune deficiency, and fetal congenital anomalies. The study was approved by the Ethics Committee for Research Involving Human Subjects, Universiti Putra Malaysia [FPSK(FR16)P006] and the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-16-1047-30685). Written informed consent was obtained from all respondents.

2.2. Serum 25-Hydroxyvitamin D [25(OH)D] Analysis

Maternal serum 25(OH)D concentrations were measured once in late pregnancy. As detailed previously [22], a venous blood sample (2 mL) was collected from pregnant women during their routine antenatal check-up by trained nursing staff at the health clinics. When their blood was collected, the gestational age of the pregnant women was recorded. The blood sample was transferred to the blood collection tube and stored in the container provided by the laboratory at 2–8 °C. Blood samples were then sent to the laboratory (Pantai Premier Pathology Sdn. Bhd., Kuala Lumpur, Malaysia) within 24 h for further analysis. At the laboratory, the blood samples were analyzed by the trained laboratory staff using the Siemens ADVIA Centaur Vitamin D Total assay (Siemens, Tarrytown, NY, USA) to determine the serum 25(OH)D concentration. This assay has been standardized to the University of Ghent ID-LC/MS/MS reference measurement procedure and certified by the CDC Vitamin D Standardization Certification program [23]. Maternal serum 25(OH)D levels were categorized as deficient (<30 nmol/L) and nondeficient (≥30 nmol/L) [24]. Results of the serum 25(OH)D analysis were given to the mothers during the first postnatal follow-up at 3 months postpartum.

2.3. Allergic Sensitization

A peripheral venous blood sample of 1–2 mL was withdrawn via venepuncture in the dorsum of an infant's hand by a trained medical assistant at the health clinic at 12 months follow-up. The blood sample was transferred into a serum separator tube and stored in the container provided by the laboratory at 2–8 °C. Blood samples were sent to the laboratory (Acutest Systems (M) Sdn. Bhd., Kuala Lumpur, Malaysia) within 24 h from the time of specimen collection for processing. The allergen-specific immunoglobulin E (IgE) levels against a panel of 19 types of food allergens (egg yolk, egg white, soybean, peanut, milk, clam, crab, shrimp, codfish, tuna, salmon, wheat, chicken, beef, rice, banana, orange, sesame seed, chocolate) and 16 types of inhalant allergens (house dust, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Blomia tropicalis*, Timothy grass, Bermuda grass, mucor, *Alternaria*, *Aspergillus*, *Candida*, *Cladosporium*, *Penicillium*, dog dander, cat dander, cockroach mix, and latex) were analyzed by the trained laboratory staff using the OPTIGEN Allergen Specific IgE Assay (Hitachi Chemical Diagnostics, Inc., Mountain View, CA). A level of specific IgE < 27 LU was rated as class 0, 27–65 LU as class 1, 66–142 LU as class 2, 143–242 LU as class 3, and >242 LU as class 4, respectively. Infants with a specific IgE level of class ≥ 1 were defined as having sensitization [25].

2.4. Allergic Outcomes

Allergic outcomes including eczema, IgE-mediated food allergy, and wheezing in infants were assessed at age 3, 6, and 12 months by trained researchers through face-to-face interviews with the mothers. Eczema was defined according to the UK Working Party's Diagnostic Criteria for Atopic Dermatitis, namely having an itchy skin condition and fulfilling two or more of the following criteria: (i) family history of allergic disease; (ii) history dry skin; (iii) history of involvement of skin creases; and (iv) visible flexural eczema [26]. Infants with parent-reported food allergy symptoms who had a specific IgE level of class ≥ 1 to a specific food allergen were defined as having IgE-mediated food allergy. Food allergy symptoms were based on convincing clinical history that encompassed three of the following criteria: (i) parent reporting at least one recognized allergic symptom, which included localized symptoms (such as itching, sting/burning of the lips/mouth/throat, urticaria/hives, angioedema), abdominal symptoms (such as nausea, vomiting, crampy/colicky abdominal pain,

diarrhea), respiratory symptoms (such as wheeze, stridor, watery rhinitis, redness of eyes/nose), skin symptoms (such as urticaria, itching, flushed skin, worsening eczema), or systemic reactions (such as anaphylaxis, syncope); (ii) parent reporting a temporal relationship of a reaction, with symptoms occurring within 2 h of food ingestion; and (iii) symptoms repeated each time the same food was consumed [2]. Wheeze was defined as the parental report of infants who had wheezing or whistling in the chest during the first year of life using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire [27].

2.5. Covariates

Information on potential confounders associated with allergic outcomes [28] was collected. Information on maternal age, work status, ethnicity, educational level, maternal gestational age at blood withdrawal, parity, gestational age at delivery, birth weight, mode of delivery, and infant sex were obtained from clinic records. Meanwhile, information on monthly household income, maternal use of antibiotics during pregnancy, number of siblings, pets at home during the first year, infants' daycare attendance during the first year, infant antibiotic use during the first year, exclusive breastfeeding, and family history of allergic disease were obtained via face-to-face interviews with the mothers. Family history of allergic disease was defined as any of the infant's first-degree relatives having one or more histories of eczema, food allergy, asthma or allergic rhinitis.

2.6. Statistical Analysis

We used a log-binomial generalized linear mixed model (GLMM) to determine the associations between maternal Vitamin D levels and allergic diseases. Analysis was performed for the 380 mother–child pairs with complete data for three follow-ups. Pregnant women with deficient Vitamin D levels were considered as the "exposed" group, while those with nondeficient Vitamin D levels were considered as the "unexposed" group. Study sites and respondents were entered as random effects. Multivariable models were adjusted for potential confounding variables significantly associated with maternal Vitamin D levels and allergic outcomes ($p < 0.05$) identified from univariable models: ethnicity, gestational age at birth, mode of delivery, and antibiotic use in infants during the first year of life. We also performed multivariable models by adjusting additional confounding factors based on conceptual justification as suggested in previous literature [28]: maternal age, ethnicity, educational level, household income, work status, parity, antibiotic use during pregnancy, family history of allergic disease, gestational age at birth, infant birth weight, mode of delivery, sex, number of siblings, pet keeping, daycare attendance, antibiotic use in infants during the first year, and exclusive breastfeeding $\geq$ 6 months. All models were adjusted for gestational age at blood withdrawal and eczema status. Risk ratios (RRs) with a 95% confidence interval (CI) were calculated as the measure of associations between maternal Vitamin D levels and allergic diseases. Statistical analyses were performed using IBM SPSS Statistics 22 software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Characteristics of the Mother–Child Pairs

Of the 535 pregnant women who consented and completed baseline data at the third trimester, 430 mother–child pairs completed the 3 month follow-up, 406 completed the 6 month follow-up, and 380 completed the 12 month follow-up (Figure 1). The reasons for dropout include respondents who moved out of the study area and were unable to be contacted (51 mother–child pairs), those unwilling to continue their participation in the study or had parental worries concerning blood taking of their child (79 mothers), preterm delivery (21 infants), infant death (2 infants), or having been diagnosed with acute illness (2 infants).

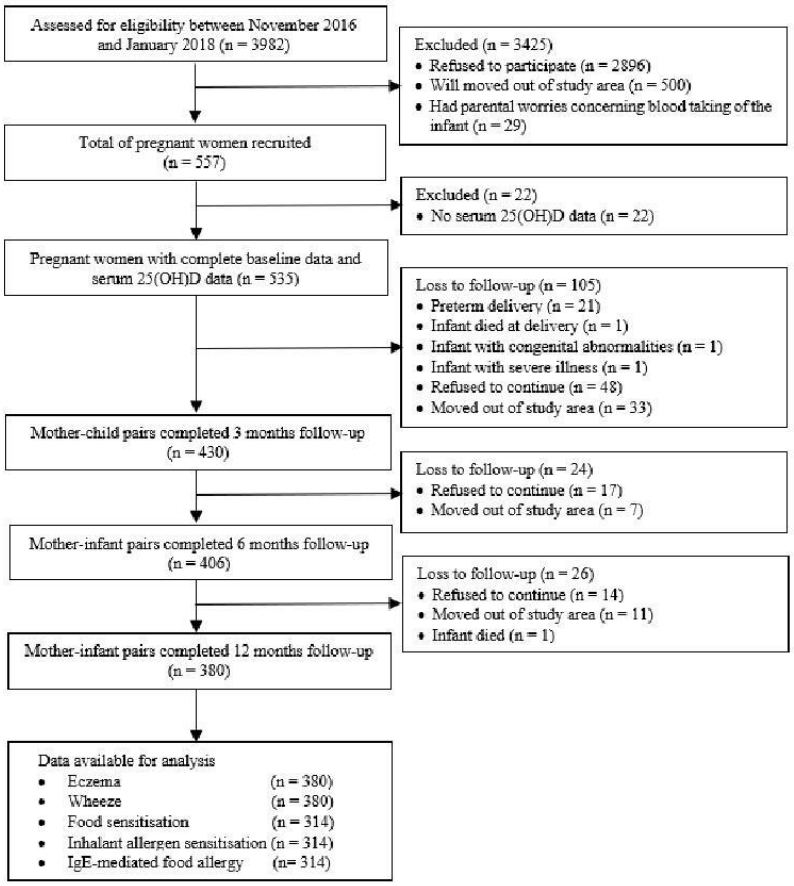

Figure 1. Flow chart of study respondents.

Table 1 presents the characteristics of the study respondents. Of the 380 pregnant women, 43.2% were Vitamin D deficient, while 56.8% were nondeficient. Overall, the final cohort of the present study is representative of the original cohort as there were no significant differences in the characteristics of the respondents in terms of maternal age, ethnicity, educational level, work status, parity, family history of allergic disease, and maternal Vitamin D status during late pregnancy between the mother–child pairs who completed the 12 month follow-up (n = 380) and those loss to follow-up (n = 155) except for with monthly household income.

Table 1. Characteristics of the mother–child pairs.

Characteristics	Total			Maternal 25(OH)D Levels		
	Included in Age 12 Month Analysis (n = 380)	Loss to Follow-Up (n = 155)	*p*-Value	Deficient < 30 nmol/L (n = 164)	Nondeficient ≥ 30 nmol/L (n = 216)	*p*-Value
Maternal 25(OH)D levels						
Deficient (<30 nmol/L)	164 (43.2)	63 (40.6)	0.594			
Nondeficient (≥30 nmol/L)	216 (56.8)	92 (59.4)				
Gestational age at blood withdrawal (weeks)						
Median (IQR)	32 (29, 36)	31 (28–35)	0.013			
Family characteristics						
Maternal age (years)	30.1 ± 4.2	29.6 ± 4.0	0.225	30.0 ± 4.0	30.2 ± 4.3	0.591
Maternal ethnicity, Malay (%)	350 (92.1)	143 (92.3)	0.952	161 (98.2)	189 (87.5)	0.001
Maternal educational level, higher (%)	312 (82.1)	126 (81.3)	0.824	129 (78.7)	183 (84.7)	0.127
Monthly household income						
Low (< RM 2300)	52 (13.7)	40 (25.8)	0.003	26 (15.9)	26 (12.0)	0.062
Moderate (RM 2300–5599)	209 (55.0)	72 (46.5)		97 (59.1)	112 (51.9)	
High (≥RM 5600)	119 (31.3)	43 (27.7)		41 (25.0)	78 (36.1)	
Maternal work status, working (%)	267 (70.3)	103 (66.5)	0.387	118 (72.0)	149 (69.0)	0.530
Parity, multiparous (%)	226 (59.5)	83 (53.5)	0.208	101 (61.6)	125 (57.9)	0.465
Family history of allergic disease, yes (%)	257 (67.6)	98 (63.2)	0.328	109 (66.5)	148 (68.5)	0.672
Maternal antibiotics use during pregnancy, yes (%)	44 (11.6)	6 (12.0) [a]	0.930	37 (22.6)	56 (25.9)	0.450
Pet keeping, yes (%)	93 (24.5)	–	–	13 (7.9)	31 (14.4)	0.053
Infant characteristics						
Gestational age at birth (weeks)	38.9 ± 1.1	38.8 ± 1.0 [a]	0.579	38.8 ± 1.1	38.9 ± 1.2	0.867
Birth weight (kg)	3.1 ± 0.4	3.1 ± 0.4 [a]	0.845	3.1 ± 0.4	3.1 ± 0.4	0.620
Mode of delivery, vaginal (%)	278 (73.2)	36 (72.0) [a]	0.862	119 (72.6)	159 (73.6)	0.819
Sex, male (%)	190 (50.0)	31 (62.0) [a]	0.110	77 (47.0)	113 (52.3)	0.300
Older siblings, yes (%)	226 (59.5)	83 (53.5)	0.208	101 (61.6)	125 (57.9)	0.465
Daycare attendance, yes (%)	207 (54.5)	–	–	82 (50.0)	125 (57.9)	0.127
Antibiotic use, yes (%)	224 (58.9)	–	–	93 (56.7)	131 (60.6)	0.439
Exclusive breastfeeding till 6 months (%)	177 (46.6)	13 (50.0) [b]	0.735	74 (45.1)	103 (47.7)	0.620

Data shown are the mean ± standard deviation for the continuous variables and number (percentage) of respondents for categorical variables. *p*-values for difference were determined by a Chi-square test for categorical variables and an independent *t*-test for two independent samples. RM, Ringgit Malaysia (1 USD = RM 4.28, as of June 23, 2020). [a] Data available for 50 mother–child pairs who completed the 3 month follow-up. [b] Data available for 26 mother–child pairs who completed the 6 month follow-up.

3.2. Allergic Outcomes in Infants

Of the 380 infants, 27.6% developed eczema and 6.1% developed wheeze, respectively, during the first year of life (Table 2). Of the 314 infants who undertook the allergen-specific IgE test at 12 months of age, 27.4% were sensitized to at least one of the food allergens tested and 10.8% were sensitized to at least one of the inhalant allergens tested. The top three food allergens sensitized by infants at 12 months of age were beef (14.3%), peanut (10.8%), and egg white (7.0%), while the top three inhalant allergens were *Dermatophagoides farinae* (6.4%), *Dermatophagoides pteronyssinus* (5.4%), and *Blomia tropicalis* (4.1%). The prevalence of IgE-mediated food allergy was 3.8%, with 3.2% egg allergy, 1.0% cow's milk allergy, 0.6% wheat allergy, and 0.3% soy allergy.

Table 2. Allergic diseases in infants during the first year of life.

Allergic Diseases	N (%)
Eczema in the past 12 months (n = 380)	105 (27.6)
Wheeze in the past 12 months (n = 380)	23 (6.1)
Food sensitization at 12 months (n = 314) [1]	86 (27.4)
Beef (n = 314)	45 (14.3)
Peanut (n = 314)	34 (10.8)
Egg white (n = 314)	22 (7.0)
Egg yolk (n = 314)	10 (3.2)
Soya (n = 314)	14 (4.5)
Cow's milk (n = 314)	7 (2.2)
Shrimp (n = 314)	6 (1.9)
Crab (n = 314)	6 (1.9)
Clam (n = 314)	4 (1.3)
Codfish (n = 314)	4 (1.3)
Wheat (n = 314)	4 (1.3)
Salmon (n = 314)	3 (1.0)
Chocolate (n = 314)	2 (0.6)
Rice (n = 314)	2 (0.6)
Tuna (n = 314)	2 (0.6)
Chicken (n = 314)	1 (0.3)
Orange (n = 314)	1 (0.3)
Inhalant allergen sensitization at 12 months (n = 314) [1]	34 (10.8)
Dermatophagoides farinae (n = 314)	20 (6.4)
Dermatophagoides pteronyssinus (n = 314)	17 (5.4)
Blomia tropicalis (n = 314)	13 (4.1)
Candida (n = 314)	7 (2.2)
Cat dander (n = 314)	7 (2.2)
House dust (n = 314)	6 (1.9)
Dog dander (n = 314)	4 (1.3)
Cockroach mix (n = 314)	4 (1.3)
Penicillium (n = 314)	3 (1.0)
Cladosporium (n = 314)	2 (0.6)
Aspergillus (n = 314)	1 (0.3)
Bermuda grass (n = 314)	1 (0.3)
IgE-mediated food allergy at 12 months (n = 314)	12 (3.8)
Eggs (n = 314)	10 (3.2)
Cow's milk (n = 314)	3 (1.0)
Wheat (n = 314)	2 (0.6)
Soy (n = 314)	1 (0.3)

Data shown are the number (percentage) of respondents. [1] Allergens with 0% respondents were not shown.

3.3. Associations between Maternal Vitamin D Levels and Allergic Diseases

Table 3 shows the associations of maternal Vitamin D levels with each of the allergic outcomes. We observed no associations of maternal Vitamin D deficient in late pregnancy with any of the allergic outcomes in infants during the first year of life, compared with the nondeficient group. These null associations remained after adjustment for potential confounding factors.

Table 3. Associations between maternal 25(OH)D levels and allergic diseases in infants during the first year of life.

Allergic Outcomes	Crude		Adjusted [1]		Adjusted [2]	
	RR (95% CI)	*p*-Value	RR (95% CI)	*p*-Value	RR (95% CI)	*p*-Value
Eczema (n = 380)						
Nondeficient (≥30 nmol/L)	1		1		1	
Deficient (<30 nmol/L)	1.02 (0.77–1.35)	0.884	1.04 (0.79–1.38)	0.770	1.10 (0.83–1.46)	0.495
Wheeze (n = 380)						
Nondeficient (≥30 nmol/L)	1		1		1	
Deficient (<30 nmol/L)	1.01 (0.48–2.13)	0.973	1.04 (0.50–2.18)	0.915	1.10 (0.61–2.00)	0.755
Food allergen sensitization (n = 314)						
Nondeficient (≥30 nmol/L)	1		1		1	
Deficient (<30 nmol/L)	1.22 (0.85–1.75)	0.282	1.08 (0.76–1.54)	0.650	1.05 (0.75–1.48)	0.782
Inhalant allergen sensitization (n = 314)						
Nondeficient (≥30 nmol/L)	1		1		1	
Deficient (<30 nmol/L)	0.58 (0.29–1.16)	0.122	0.58 (0.29–1.15)	0.121	0.59 (0.29–1.19)	0.137
IgE-mediated food allergy (n = 314)						
Nondeficient (≥30 nmol/L)	1		1		1	
Deficient (<30 nmol/L)	0.54 (0.18–1.62)	0.269	0.64 (0.30–1.40)	0.268	0.68 (0.31–1.53)	0.355

CI, confidence interval; RR, relative risk. [1] Model was adjusted for ethnicity, gestational age at blood withdrawal, gestational age at birth, mode of delivery, and antibiotic use in infants during the first year. [2] Model was adjusted for maternal age, ethnicity, educational level, household income, work status, parity, antibiotic use during pregnancy, gestational age at blood withdrawal, family history of allergic disease, gestational age at birth, infant birth weight, mode of delivery, sex, number of siblings, pet keeping, daycare attendance, antibiotic use during the first year, and exclusive breastfeeding ≥ 6 months. Food allergy, wheeze, and allergen sensitization outcomes were adjusted for eczema status.

4. Discussion

The results of this prospective cohort study suggest that maternal Vitamin D levels in late pregnancy were not associated with offspring eczema, wheeze, food sensitization, inhalant allergen sensitization, and IgE-mediated food allergy during the first year of life when adjusted for a range of potential confounding factors.

The prevalence of infantile eczema (27.6%), wheezing (6.1%), and inhalant allergen sensitization (10.8%) in the present study is comparable with the parent-reported eczema (20.9%), wheezing (9.8%), and aeroallergen sensitization (11.2%) in infants at 18 months of age in the Singapore GUSTO cohort study [29,30]. Similarly, the IgE-mediated food allergy prevalence (3.8%) in the present study is in line with the prevalence of IgE-mediated food allergy (2.9%) in Singaporean infants aged 12 months [31]. Our study suggests that Malaysian children are at high risk of developing allergies in early life, and these health issues should be given special attention by health professionals.

Studies that assessed the associations between maternal Vitamin D levels and childhood food allergy and sensitization reported inconsistent results [10,11,15,32]. The Taiwan PATCH cohort study found that high maternal Vitamin D levels (≥75 nmol/L) were protective against food sensitization in children at age 1.5 and 2 years [10]. In contrast, the German LINA cohort study revealed that higher maternal Vitamin D levels were associated with an increased risk of food allergy and food sensitization in children at the age of 2 years [11]. In line with our findings, the Cork BASELINE birth cohort and the GUSTO study found that maternal Vitamin D levels were not associated with childhood food allergy food sensitization [15,32]. Similar findings were reported in an RCT conducted in the UK that failed to detect an effect of prenatal Vitamin D supplementation on the risk of food allergy in infants at 3 years of age [16]. It should be noted that the comparison of findings across studies might be difficult due to differences in terms of length of follow-up, the period of pregnancy at which maternal Vitamin D levels were measured, methods of food allergy and food sensitization measurement such as physician-diagnosed food allergy [11,15], skin prick test [15,32], or specific IgE-confirmed food

sensitization [10]. In the present study, we did not observe an association between maternal Vitamin D levels and childhood food allergy, and we therefore speculate that other factors such as genetic factors may play a more important role in explaining this association. The Boston birth cohort conducted by Liu et al. [33] showed that cord blood Vitamin D levels were not associated with food sensitization in early childhood; however, a significant inverse association was found in children with particular genotypes. Therefore, further studies are needed to explore the interactions between genetic factors and Vitamin D levels in explaining their relationships with childhood food allergy.

There is lack of consistent findings addressing the associations between maternal Vitamin D levels and childhood eczema [14,15,32,34]. The inconsistent findings may be explained by the "U-shape" associations, suggesting that both lower and higher levels of Vitamin D are associated with a higher risk of eczema [14,34]. The UK birth cohort found that maternal 25(OH)D concentrations > 75 nmol/L were associated with increased offspring eczema risks at 9 months of age [14]. Another study reported that mid-pregnancy 25(OH)D concentrations < 25 nmol/L were associated with the increased risk of eczema in children ≤ 3 years of age [34]. In contrast, we found no associations between maternal Vitamin D levels and the development of eczema in childhood, which is in line with the findings reported in the Cork BASELINE birth cohort [15] and the Generation R study [35]. Similarly, results from several RCTs have not found a protective role of maternal Vitamin D supplementation during pregnancy in the risk of eczema in infants and children [16–19]. Apart from methodological differences across studies, the null associations between maternal Vitamin D levels and eczema in the present study may be explained by genetic factors, which play a more important role in the development of childhood eczema. Evidence showed that mutations in the filaggrin gene have been strongly associated with the development of eczema [36,37]. Therefore, the potential for Vitamin D to interact with genetic factors in explaining the development of childhood eczema should be considered in future studies.

Consistent with previous studies [20,38,39], we found no associations between maternal Vitamin D levels in late pregnancy and wheeze and inhalant allergen sensitization in infants during the first year of life. Similarly, findings from several RCTs showed that maternal Vitamin D supplementation during pregnancy did not pose an effect on the development of wheeze and inhalant allergen sensitization in infants during the first 3 years of life [16–20]. In contrast to our findings, Rothers et al. [40] reported that both low (<50 nmol/L) and high (>100 nmol/L) levels of cord blood Vitamin D levels were associated with increased specific IgE levels with certain inhalant allergens in children at 5 years of age. Another study demonstrated that low maternal Vitamin D levels (<50 nmol/L) were associated with the higher risk of aeroallergen sensitization during the first 2 years of life [10]. As findings from the birth cohorts are inconsistent and previous RCTs failed to demonstrate the protective role of prenatal Vitamin D supplementation on wheeze and inhalant allergen sensitization in infants, further studies are needed to determine the combined effects of prenatal and postnatal Vitamin D status on the development of allergic diseases in offspring.

To the best of knowledge, the present study is the first prospective cohort study to report the relationship between maternal Vitamin D levels and infants' allergic outcomes in Malaysia. The strengths of our study include a longitudinal study design which enables information on a large number of potential confounders to be recorded and adjusted in multivariable analyses. Parental reports of allergic outcomes, rather than direct assessment by physicians, are the major limitation of this study. Previous studies have demonstrated that both lower and higher maternal Vitamin D levels were associated with an increased risk of allergic diseases in offspring [14,34,40]. In the present study, we managed to determine the associations between low levels of maternal Vitamin D and infants' allergic outcomes but were unable to assess the outcomes for high maternal Vitamin D levels due to low numbers of pregnant women with sufficient Vitamin D levels, which may lead to insufficient statistical power to detect significant associations with allergic outcomes. Similarly, the low number of infants with wheeze and IgE-mediated food allergy reported in the present study may lead to insufficient statistical power to detect their associations with maternal Vitamin D levels. Attrition is a concern in prospective cohort studies which may lead to selection bias. However, there were no

significant differences in the majority of the characteristics between the respondents who completed the study and those loss to follow-up, suggesting limited bias. The present study was able to report the relationship between low Vitamin D levels in the third trimester pregnant mothers and allergic disease development in infants from Selangor and Kuala Lumpur—the two most urbanized states in Malaysia. However, the findings might not be generalizable to the other populations. In the present study, maternal Vitamin D levels were measured once in late pregnancy, as evidence has shown that maternal 25(OH)D levels were the highest in late pregnancy and were associated with infants' serum 25(OH)D [41–43]. However, our study was unable to determine the changes in maternal Vitamin D levels over the course of pregnancy and their effects on the study outcomes.

5. Conclusions

In conclusion, our results suggest that maternal Vitamin D levels in late pregnancy are not associated with allergic outcomes in infants during the first year of life. Further studies are needed to explore the role of Vitamin D in childhood allergies in combination with other environmental and genetic factors.

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Appendices

Appendix 13: Additional Analyses

Multiple imputation was performed to impute missing data on independent, dependent, and confounding variables by using chained equations. Fifty imputed data sets were generated (Graham, Olchowski, & Gilreath, 2007) and used to repeat all analyses. The imputed data were analyzed using statistical software R (Version 4.0.2, 2020, http://www.R-project.org/). As shown in Table 13.1, there were no significant associations of maternal vitamin D status during late pregnancy and infant feeding practices with allergic diseases in infants during the first year of life after adjustment of confounding factors. Similarly, no associations were found between maternal vitamin D status and infant feeding practices with malnutrition (Table 13.2) and growth indicators (Table 13.3) in infants at 12 months of age after adjustment for confounding factors.

Table 13.1. Multivariable model of associations of maternal vitamin D status during late pregnancy and infant feeding practices with allergic diseases in infants during the first year of life (N = 512)

Variable	Allergic diseases during first year of life			
	Eczema	Parent-reported food allergy	Food sensitisation	IgE-mediated food allergy
	95% CI	95% CI	95% CI	95% CI
Vitamin D status during pregnancy				
≥ 30 nmol/L	1	1	1	1
< 30 nmol/L	-0.51, 0.39	-0.17, 0.86	-0.30, 0.65	-0.84, 0.51
Exclusive breastfeeding				
Not met	1	1	1	1
Met	-0.47, 0.72	-0.43, 0.91	-0.72, 0.41	-1.02, 0.67
Introduction of complementary foods				
Met	1	1	1	1
Not met	-0.21, 2.27	-1.43, 2.83	-2.07, 2.61	-1.10, 2.81
MDD at 6 months				
Not met	1	1	1	1
Met	-0.56, 1.49	-0.55, 1.66	-0.67, 1.57	-1.22, 1.67

Note: Health clinics and mother-infant pairs were entered as random effects. Models were adjusted for family history of allergic diseases, maternal age, gestational age at blood withdrawal, mode of delivery, and number of siblings. GLMM for eczema was adjusted for the aforementioned confounding factors and food allergy. GLMM for food allergy and food sensitisation was adjusted for the aforementioned confounding factors and eczema. 95% CI that does not cover zero indicates significant associations.

Table 13.2. Multivariable model of associations of maternal vitamin D status during late pregnancy and infant feeding practices with malnutrition in infants during the first year of life (N = 512)

Variable	Malnutrition during first year of life			
	Stunting	Wasting	Underweight	Overweight
	95% CI	95% CI	95% CI	95% CI
Vitamin D status during pregnancy				
≥ 30 nmol/L	1	1	1	1
< 30 nmol/L	-0.50. 0.54	-0.68, 0.54	-0.50, 0.61	-0.75, 0.84
Exclusive breastfeeding				
Not met	1	1	1	1
Met	-0.54, 1.01	0.25, 1.14	-0.43, 1.09	-1.40, 1.01
Introduction of complementary foods				
Met	1	1	1	1
Not met	--0.36, 2.74	01.12, 3.54	-1.62, 3.67	-0.33, 3.52
MDD at 6 months				
Not met	1	1	1	1
Met	-0.90, 1.76	-0.36, 1.87	-0.87, 1.95	-1.08, 2.67

Note: Health clinics and mother-infant pairs were entered as random effects. Models were adjusted for maternal educational level, monthly household income, gestational age at blood withdrawal, parity, infant's sex, and birth weight. 95% CI that does not cover zero indicates significant associations.

Multivariable LMM using the imputed dataset shows that compliances to WHO recommendations for exclusive breastfeeding until 6 months were associated with decreased WAZ and LAZ in infants at 12 months of age (Table 13.3).

Table 13.3. Multivariable LMM of associations of maternal vitamin D status during late pregnancy and infant feeding practices with growth indicators in infants during the first year of life (N = 512)

Variable	Growth indicators during first year of life			
	WAZ	LAZ	WLZ	BAZ
	B (95% CI)	B (95% CI)	B (95% CI)	B (95% CI)
Vitamin D status during pregnancy				
≥ 30 nmol/L	1	1	1	1
< 30 nmol/L	0.07 (-0.12, 0.26)	-0.003 (-0.23, 0.22)	0.08 (-0.14, 0.30)	0.11 (-0.11, 0.34)
Exclusive breastfeeding				
Not met	1	1	1	1
Met	-0.26 (-0.46. -0.06)*	-0.26 (-0.51, -0.003)*	-0.17 (-0.41, 0.06)	-0.15 (-0.38, 0.09)
Introduction of complementary foods				
Met	1	1	1	1
Not met	-0.05 (-0.51, 0.40)	-0.10 (-0.69, 0.50)	0.04 (-0.49, 0.57)	0.02 (-0.51, 0.55)
MDD at 6 months				
Not met	1	1	1	1
Met	-0.04 (0.34, 0.25)	0.04 (-0.39, 0.46)	-0.11 (-0.49, 0.28)	-0.09 (-0.48, 0.29)

Note: Health clinics and mother-infant pairs were entered as random effects. Models were adjusted for maternal age, gestational age at blood withdrawal, parity, gestational weight gain, infant's sex, and birthweight. *p < 0.05.

Catch-up growth was defined as a change in WAZ ⩾ 0.67 during the first 6 months of life (Ong et al., 2000). Table 13.4 shows the multivariable GLMM of associations of maternal vitamin D status and infant feeding practices with allergic diseases, with catch-up growth adjusted in the model. After adjustment for confounding factors, maternal vitamin D deficiency during pregnancy was associated with higher odds of parent-reported food allergy in infants, while infants who met the MDD at 6 months were 2.26 times more likely to have food sensitisation at 12 months of age. No associations were found between maternal vitamin D status and infant feeding practices with all forms of malnutrition (Table 13.5).

Table 13.4. Multivariable GLMM of associations of maternal vitamin D status during late pregnancy and infant feeding practices with allergic diseases in infants (N = 380)

Variable	Allergic diseases during first year of life			
	Eczema	Parent-reported food allergy	Food sensitisation	IgE-mediated food allergy
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Vitamin D status during pregnancy				
≥ 30 nmol/L	1	1	1	1
< 30 nmol/L	0.85 (0.52-1.40)	1.76 (1.01-3.05)*	1.32 (0.78-2.24)	0.68 (0.25-1.89)
Exclusive breastfeeding				
Not met	1	1	1	1
Met	1.19 (0.72-1.99)	1.43 (0.79-2.57)	0.80 (0.46-1.41)	1.11, 0.40-3.10)
Introduction of complementary foods				
Met	1	1	1	1
Not met	0.36 (0.04-2.99)	0.44 (0.05-4.00)	1.56 (0.36-6.77)	0.59 (0.01-27.05)
MDD at 6 months				
Not met	1	1	1	1
Met	1.56 (0.72-3.37)	1.61 (0.67-3.86)	2.26 (0.99-5.12)*	0.47 (0.06-3.68)

Note: Health clinics and mother-infant pairs were entered as random effects. Models were adjusted for family history of allergic diseases, maternal age, gestational age at blood withdrawal, mode of delivery, number of siblings, and catch-up growth. GLMM for eczema was adjusted for the aforementioned confounding factors and food allergy. GLMM for food allergy and food sensitisation was adjusted for the aforementioned confounding factors and eczema. * p < 0.05.

Table 13.5. Multivariable GLMM of associations of maternal vitamin D status during late pregnancy and infant feeding practices with malnutrition in infants (N = 380)

Variable	Allergic diseases during first year of life			
	Stunting	Wasting	Underweight	Overweight
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Vitamin D status during pregnancy				
≥ 30 nmol/L	1	1	1	1
< 30 nmol/L	0.99 (0.55-1.78)	0.77 (0.36-1.65)	0.96 (0.50-1.84)	1.00 (0.35-2.83)
Exclusive breastfeeding				
Not met	1	1	1	1
Met	1.71 (0.92-3.19)	1.57 (0.72-3.41)	1.79 (0.90-3.56)	1.00 (0.34-3.00)
Introduction of complementary foods				
Met	1	1	1	1
Not met	3.18 (0.74-13.78)	0.41 (0.01-13.49)	0.44 (0.01-14.31)	0.57 (0.02-20.17)
MDD at 6 months				
Not met	1	1	1	1
Met	0.84 (0.29-2.38)	0.93 (0.27-3.28)	0.62 (0.18-2.13)	0.92 (0.13-6.65)

Note: Health clinics and mother-infant pairs were entered as random effects. Models were adjusted for maternal educational level, monthly household income, gestational age at blood withdrawal, parity, infant's sex, birth weight, and catch-up growth. * $p < 0.05$.

Table 13.6 and Table 13.7 shows the multivariable GLMM of associations of maternal vitamin D status (continuous scale) and infant feeding practices with allergic diseases and malnutrition. After adjustment for confounding factors, no associations were found between maternal vitamin D status (continuous scale) with allergic diseases and malnutiriton in infants.

Table 13.6. Multivariable GLMM of associations of maternal vitamin D status during late pregnancy and infant feeding practices with allergic diseases in infants

Variable	Allergic diseases during first year of life			
	Eczema	Parent-reported food allergy	Food sensitisation	IgE-mediated food allergy
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Vitamin D status during pregnancy	1.01 (0.99-1.02)	0.99 (0.96-1.00)	0.98 (0.96-1.00)	0.99 (0.96-1.03)
Exclusive breastfeeding				
Not met	1	1	1	1
Met	1.19 (0.72-1.98)	1.48 (0.82-2.67)	0.83 (0.48-1.46)	1.13 (0.41-3.16)
Introduction of complementary foods				
Met	1	1	1	1
Not met	0.37 (0.05-3.01)	0.47 (0.05-4.21)	1.61 (0.36-7.12)	0.66 (0.01-31.83)
MDD at 6 months				
Not met	1	1	1	1
Met	1.55 (0.72-3.34)	1.77 (0.74-4.24)	2.44 (1.07-5.56)*	0.50 (0.06-3.91)

Note: Health clinics and mother-infant pairs were entered as random effects. Models were adjusted for family history of allergic diseases, maternal age, gestational age at blood withdrawal, mode of delivery, and number of siblings. GLMM for eczema was adjusted for the aforementioned confounding factors and food allergy. GLMM for food allergy and food sensitisation was adjusted for the aforementioned confounding factors and eczema. * $p < 0.05$.

Table 13.7. Multivariable GLMM of associations of maternal vitamin D status during late pregnancy and infant feeding practices with malnutrition in infants

Variable	Allergic diseases during first year of life			
	Stunting	Wasting	Underweight	Overweight
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Vitamin D status during pregnancy	1.01 (0.99-1.02)	1.01 (0.99-1.04)	1.00 (0.98-1.02)	0.99 (0.95-1.04)
Exclusive breastfeeding				
Not met	1	1	1	1
Met	1.73 (0.93-3.20)	1.58 (0.72-3.48)	1.83 (0.92-3.63)	1.00 (0.34-3.00)
Introduction of complementary foods				
Met	1	1	1	1
Not met	3.13 (0.73-13.32)	0.40 (0.01-14.06)	0.37 (0.01-11.05)	0.57 (0.02-21.00)
MDD at 6 months				
Not met	1	1	1	1
Met	0.92 (0.33-2.60)	1.13 (0.32-3.93)	0.75 (0.22-2.55)	0.81 (0.11-5.85)

Note: Health clinics and mother-infant pairs were entered as random effects. Models were adjusted for maternal educational level, monthly household income, gestational age at blood withdrawal, parity, infant's sex, and birth weight. * $p < 0.05$.

Biodata of the Student

Woon Fui Chee is a PhD candidate under a joint PhD program between the Universiti Putra Malaysia and University of Wollongong, majoring in Community Nutrition. Her doctoral research investigates the role of maternal vitamin D status during late pregnancy and feeding practices on the development of allergic diseases and malnutrition in early childhood. She holds a master's degree in Science, majoring in Community Nutrition from Universiti Putra Malaysia in 2014, that investigated the associations between home environment, behavioural factors, and body weight status among early adolescents in Malaysia. She received her first-class honours bachelor's degree in Biology from Universiti Putra Malaysia in 2011, that investigated the effects of pharmacophagy ethyl vanillate on the attraction of fruit flies to conspecific males and mating competition.

She is a member of the Nutrition Society of Malaysia since 2012 and the Malaysian Association for the Study of Obesity since 2014. In addition, she is a qualified level one anthropometrist recognised by the International Society for the Advancement of Kinanthropometry (ISAK). She is the recipient of Graduated Research Fellowship in 2011 and Research University Grant Scheme in 2012 awarded by Universiti Putra Malaysia. She was also awarded the MyBrain Scholarship by Ministry of Higher Education Malaysia to further her doctoral degree in 2014. In 2016, she was selected to participate in the Young Scholars Program (YSP) organised by the Higher Education Leadership Academy Malaysia along with 19 other postgraduates selected from all public universities in Malaysia. She is also one of the 17 selected recipients of the DuPont Nutrition and Health Competitive Grant for Young Nutrition Leaders to attend the International Young Food and Nutrition Leadership (iYouLead) programme in Bali, Indonesia.

During her candidature, she worked as a research assistant and project manager for a few large-scale studies, organising committee member for seminars and training, and nutrition counsellor in public events. She has published articles in several international and local peer-reviewed journals and presented her studies in national and international conferences.

List of Publications

The findings of this thesis have been prepared for publication as follows:

Peer Reviewed Publications

1. Woon, F. C., Chin, Y. S., Intan, H. I., Chan, Y. M., Batterham, M., Amir Hamzah, A. L., …Geeta, A. (2018). Contribution of early nutrition on the development of malnutrition and allergic diseases in the first year of life: a study protocol for the Mother and Infant Cohort Study (MICOS). *BMC Pediatrics, 18*, 233. doi: 10.1186/s12887-018-1219-3 (Appendix 1)
2. Woon, F. C., Chin, Y. S., Intan, H. I., Batterham, M., Amir Hamzah, A. L., Gan, W. Y., …Chan, Y. M. (2019). Vitamin D deficiency during pregnancy and its associated factors among third trimester Malaysian pregnant women. *PLOS One, 14*(6), e0216439. doi: 10.1371/journal.pone. 0216439 (Appendix 11)
3. Woon, F. C., Chin, Y. S., Intan Hakimah, I., Amir Hamzah, A. L., Batterham, M., Chan, Y. M., & the MICOS Research Group. (2020). Maternal vitamin D levels during late pregnancy and risk of allergic diseases and sensitization during the first year of life - a birth cohort study. *Nutrients, 12,* 2418. doi: 10.3390/nu12082418 (Appendix 12)

Manuscripts in Preparation

1. Woon, F. C., Chin, Y. S., Intan Hakimah, I., Amir Hamzah, A. L., Batterham, M., Chan, Y. M., & the MICOS Research Group. (2020). Associations between infant feeding practices and allergic diseases in infants during the first year of life. To be submitted to Nutrients.
2. Woon, F. C., Chin, Y. S., Intan Hakimah, H. I., Amir Hamzah, A. L., Batterham, M., Chan, Y. M., & the MICOS Research Group. (2020). Associations between allergic diseases and malnutrition in infants during the first year of life. To be submitted to BMC Pediatrics.

Conference Abstracts

1. Woon, F. C., Chin, Y. S., Intan Hakimah, I., Chan, Y. M., Amir Hamzah, A. L., Gan, W. Y., …Batterham, M. (2019). Risk factors for vitamin D deficiency among third-trimester Malaysian pregnant women: findings from the Mother and Infant Cohort Study (MICOS). Oral presentation. Asian Congress of Nutrition. 4-7 August 2019, Bali International Convention Center, Bali, Indonesia.
2. Woon, F. C., Chin, Y. S., Intan Hakimah, I., Chan, Y. M., Amir Hamzah, A. L., Gan, W. Y., Batterham, M. (2019). Breastfeeding and food allergy in infants - findings from the Mother and Infant Cohort Study (MICOS) Malaysia. Oral presentation. DOHaD World Congress. 20-23 October 2019, Melbourne Convention and Exhibition Centre, South Wharf, Victoria, Australia.

Other Publications and Conference Abstracts

The publications and conference abstracts are not directly related to the outcomes of this thesis but were completed during the candidature:

1. Woon, F. C., Yu, M. S., & Chin, Y. S. (2018). Factors associated with rates of gestational weight gain among pregnant women in Batu Pahat district, Malaysia. *Malaysian Journal of Medicine & Health Sciences, 15*(1), 33-39.
2. Chin, Y. S., Woon, F. C., Intan Hakimah, I., Chan, Y. M., Batterham, M., Amir Hamzah, A. L., …Geeta, A. (2018). Mother and Infant cohort study (MICOS): study rationale and preliminary findings on vitamin D levels among third-trimester Malaysian pregnant mothers. Poster Presentation. 33rd NSM Scientific Conference. 24-26 July 2018, Hotel Istana, Kuala Lumpur, Malaysia.
3. Woon, F. C., Chin, Y. S., Intan Hakimah, I., Chan, Y. M., Amir Hamzah, A. L., Gan, W. Y., …Batterham, M. (2019). Risk factors and pregnancy outcomes of inappropriate gestational weight gain: findings from the Mother and Infant Cohort Study (MICOS). Oral Presentation. 1st ASEAN Nutrition and Food Science Network (ANFSN) meeting, 10-11th October, 2019, Park Rochester Hotel, Singapore.
4. Chin, Y. S., Woon, F. C., Intan Hakimah, I., Chan, Y. M., Amir Hamzah, A. L., Gan, W. Y., …Batterham, M. (2019). Association between pre-pregnancy overweight and obesity with pregnancy outcomes: findings from the Mother and Infant Cohort Study (MICOS) Malaysia. Poster Presentation. DOHaD World Congress. 20-23 October 2019, Melbourne Convention and Exhibition Centre, South Wharf, Victoria, Australia.