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RELATIONSHIPS OF MATERNAL VITAMIN D STATUS AND FEEDING PRACTICES WITH DEVELOPMENT OF ALLERGIC DISEASES AND MALNUTRITION AMONG INFANTS

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By

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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.

In this prospective cohort study, 535 third-trimester pregnant women were recruited from six selected government health clinics at the state of Selangor and Federal Territory of Kuala Lumpur, Malaysia. Their blood sample was collected to determine their serum 25(OH)D concentrations. After delivery, 380 mother-infant pairs completed the 3, 6, and 12 months follow-up. At each follow-up, infant feeding practices and allergic outcomes were assessed based on parental reports. Infant's anthropometric data were extracted from medical records. 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. About 46.6% of the infants were exclusively breastfed until 6 months, 97.1% had timely initiation of complementary feeding, 10.5% met minimum dietary diversity (MDD) at 6 months, and 54.5% met MDD at 12 months. About 27.6% of the infants had eczema, 20.8% had parent-reported food allergy (FA), 3.8% had IgE-mediated FA, 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 adjustment for confounders, study sites, and mother-infant pairs clustering effect, results from a multivariable generalised linear mixed model showed that maternal vitamin D deficiency was associated with higher odds of parent-reported FA in infants (OR = 1.82, 95% CI = 1.02-3.23). Higher odds of food sensitisation were found in infants who met MDD at 6 months (OR = 2.62, 95% CI = 1.10-6.24). No associations were found for maternal vitamin D status and other feeding practices with eczema, IgE-mediated FA, and malnutrition. Parent-reported FA was associated with higher odds of wasting in infants (OR = 2.60, 95% CI = 1.17-5.79), while no associations were found for other allergic outcomes with malnutrition. Results from the structural equation modelling showed that the relationships between maternal vitamin D deficiency (-0.29, 95% CrI = -0.55, -0.05) and wasting in infants (0.27, 95% CrI = 0.07, 0.51) were fully mediated by parent-reported FA after adjustment for confounders.

In conclusion, the present study demonstrates the important role of parent-reported FA as a mediator in explaining the relationships between maternal vitamin D deficiency during late pregnancy and wasting in infants during the first year of life. The present study suggests that nutrition education and counselling for pregnant women and lactating mothers should emphasise on the importance of vitamin D and their sources, common food allergens, and management of FA to ensure optimal growth in infants.

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

HUBUNGAN ANTARA STATUS VITAMIN D IBU DAN AMALAN PEMBERIAN MAKANAN DENGAN PEMBENTUKAN PENYAKIT ALERGI DAN MALNUTRISI DALAM KALANGAN BAYI

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Penyakit alergi dan malnutrisi merupakan dua masalah kesihatan yang paling biasa dan paling awal berlaku pada zaman awal kanak-kanak. Prevalen penyakit alergi dan malnutrisi yang tinggi amat membimbangkan disebabkan oleh implikasinya terhadap kesihatan jangka panjang dan kesejahteraan bayi. Kajian ini bertujuan untuk mengenalpasti perkaitan antara status vitamin D ibu semasa peringkat akhir dan amalan pemberian pemakanan terhadap pembentukan penyakit alergi dan malnutrisi dalam kalangan bayi semasa tahun pertama kehidupan.

Dalam kajian kohort prospektif ini, 535 wanita hamil dalam trimester ketiga direkrut dari enam klinik kesihatan kerajaan terpilih di negeri Selangor dan Wilayah Persekutuan Kuala Lumpur, Malaysia. Sampel darah mereka dikumpulkan untuk menentukan kepekatan serum 25(OH)D. Selepas bersalin, 380 pasangan ibu-bayi menyelesaikan kajian susulan pada 3, 6, dan 12 bulan. Pada setiap susulan, amalan pemberian pemakanan dan gejala alergi bayi dikaji berdasarkan laporan ibu bapa. Data antropometrik bayi diekstrak daripada rekod perubatan. Pada umur 12 bulan, sampel darah dikumpulkan daripada bayi untuk menentukan kepekaan mereka terhadap alergen makanan.

Ketidakcukupan dan kekurangan vitamin D didapati dalam 48.8% dan 42.8% wanita hamil masing-masing. Seramai 46.6% bayi diberi susu ibu secara eksklusif sehingga 6 bulan, 97.1% memulakan makanan pelengkap tepat pada waktunya, 10.5% mencapai kepelbagaian diet minimum (MDD) pada 6 bulan, dan 54.5% mencapai MDD pada 12 bulan. Sebanyak 27.6% bayi menghidapi ekzema, 20.8% menghidapi alergi makanan yang dilaporkan oleh ibu bapa,

3.8% menghidapi alergi makanan yang dimediasi oleh IgE, dan 27.4% mempunyai kepekaan makanan pada tahun pertama kehidupan. Prevalen pertumbuhan terbantut, pertumbuhan tersusut, kekurangan berat badan, dan berat badan berlebihan pada 12 bulan masing-masing adalah 16.3%, 7.6%, 11.6%, dan 1.8%. Selepas penyelarasan faktor-faktor pencetusan dan kesan kluster tapak kajian dan pasangan ibu-bayi, keputusan daripada model linear bercampur umum menunjukkan bahawa kekurangan vitamin D ibu dikaitkan dengan kemungkinan alergi makanan yang dilaporkan oleh ibu bapa yang lebih tinggi dalam kalangan bayi (OR = 1.82, 95% CI = 1.02-3.23). Risiko kepekaan makanan yang lebih tinggi didapati dalam kalangan bayi yang mencapai MDD pada 6 bulan (OR = 2.62, 95% CI = 1.10-6.24). Tiada perkaitan ditemui untuk status vitamin D ibu dan amalan pemberian makanan lain dengan ekzema, alergi makanan yang dimediasi oleh IgE, dan malnutrisi. Alergi makanan yang dilaporkan oleh ibu bapa dikaitkan dengan kemungkinan pertumbuhan tersusut yang lebih tinggi dalam kalangan bayi (OR = 2.69, 95% CI = 1.17-5.79), sementara itu tiada perkaitan didapati untuk masalah alergi dan malnutrisi yang lain. Keputusan daripada pemodelan struktur persamaan menunjukkan bahawa perhubungan antara kekurangan vitamin D ibu (-0.29, 95% CrI = -0.55, -0.05) dan pertumbuhan tersusut dalam kalangan bayi (0.27, 95% CrI = 0.07, 0.51) dimediasi sepenuhnya oleh alergi makanan yang dilaporkan oleh ibu bapa selepas penyelarasan faktor-faktor pencetusan.

Kesimpulannya, kajian ini menunjukkan peranan penting alergi makanan yang dilaporkan oleh ibu bapa sebagai pengantara dalam menjelaskan perhubungan antara kekurangan vitamin D ibu semasa peringkat akhir dan pertumbuhan terbantut dalam kalangan bayi pada tahun pertama kehidupan. Kajian ini mencadangkan bahawa pendidikan dan kaunseling pemakanan untuk wanita hamil dan ibu menyusu harus menekankan kepentingan vitamin D dan sumbernya, allergen makanan biasa, dan pengurusan alergi makanan untuk memastikan pertumbuhan optimum dalam kalangan bayi.

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Thank you.

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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
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
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
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

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). Evidence suggest that rapid weight gain during the first year of life increased the risk of obesity, high blood pressure, and diabetes in later life (Fabricius-Bjerre et al., 2011; Li, Lin, & Chiang, 2020; Perng et al., 2016). 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 et al., 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 (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 (Alam et al., 2020; Chidumwa et al., 2020; De Lucia Rolfe et al., 2018).

Vitamin D is an essential fat-soluble vitamin or steroid prohormone, which plays an important role in the regulation of calcium and phosphorus homeostasis and bone mineralization (Vanchinathan & Lim, 2012). Though there is no consensus on optimal vitamin D levels, vitamin D inadequacy (<50 nmol/L) has been identified as a global health problem and is one of the common micronutrient deficiencies during pregnancy (Fiscaletti, Stewart, & Munns, 2017). The prevalence of maternal vitamin D inadequacy during pregnancy ranges 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 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). Findings from several birth cohorts suggested that maternal vitamin D status might play a role in the

development of childhood allergic diseases and malnutrition (Blomberg et al., 2017; Chiu et al.,2015; Morales et al., 2015; Toko et al., 2016).

Apart from maternal vitamin D status, 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). World Health Organisation (WHO) 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. Globally, while more than half of infants below 6 months 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). There is evidence that non-compliance with the WHO recommendations for optimal infant feeding may increase the risk of allergic diseases and malnutrition in infants (Gao et al., 2019; Huynh, Huynh, Nguyen, Do, & Khanh Tran, 2019; Roduit et al., 2014; Udoh & Amodu, 2016).

1.2 Problem Statement

The prevalence of allergic diseases which was 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, including 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 allergic diseases 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%) (IPH, 2015), there has been a significant increase in the under-five prevalence of undernutrition in NHMS 2019, while the prevalence of overweight has reduced by 1.1% (IHSR, 2020). 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.

Research suggests that both allergic diseases and malnutrition can occur simultaneously in children and are interrelated (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 therefore important to identify their shared risk and protective factors, which may be targeted in future prevention strategies and break the vicious cycle of allergic diseases and malnutrition.

Despite the abundance of sunlight in Malaysia, a tropical country located right next to the equator, a high prevalence of vitamin D inadequacy has been reported among Malaysian pregnant women (Jan Mohamed, Rowan, Fong, & Loy, 2014; Lee et al., 2020). Different prevalence of maternal vitamin D inadequacy has been reported across states, ranged from 37.0% in the state of Kelantan (Jan Mohamed et al., 2014) to 82.2% in the state of Selangor (Lee et al., 2020). Results from several birth cohorts demonstrate the role of maternal vitamin D levels in the development of allergic diseases and malnutrition in their offspring (Chiu et al., 2015; Morales et al., 2015; Toko et al., 2016; Weisse et al., 2013). While the Taiwan birth cohort found that high maternal vitamin D levels are protective against food sensitisation in children at 2 years of age and eczema at 4 years of age (Chiu et al., 2015), the Germany birth cohort reported that high maternal vitamin D levels increased the risks of food allergy and food sensitisation in infants at 2 years of age (Weisse et al., 2013). In terms of malnutrition, Toko et al. (2016) found that infants of mothers with low vitamin D levels during pregnancy were more likely to become stunted at birth in a prospective cohort study conducted in Kenya. Meanwhile, the Spanish birth cohort showed that low maternal vitamin D levels were associated with increased risk of overweight in infants at 1 year of age (Morales et al., 2015).

Considering the potential associations between maternal vitamin D levels and the risk of childhood allergy and malnutrition, the high prevalence of vitamin D inadequacy reported among pregnant women in Malaysia may increase the risk of allergy and malnutrition development in their children. As currently no study has examined the associations of maternal vitamin D levels with the development of allergic diseases and malnutrition in infants in this country, more studies are therefore needed to assess these associations in the context of Malaysia.

Despite the importance of compliance with WHO recommendations for optimum infant feeding to promote healthy growth and development in infants and young children (WHO, 2009; WHO/UNICEF, 2003), the latest National Health and Morbidity Survey reported that more than half of the Malaysian infants under 6 months of age (52.9%) were not been on exclusively breastfed (IPH, 2016a). While the information on prevalence of complementary food introduction was not available, 33.6% of the Malaysian infants aged 6-24 months did not meet the minimum dietary diversity (IPH, 2016a). While the role infant feeding practices on childhood allergy and malnutrition has been extensively studied (Goldsmith et al., 2016; Mannan, 2018; Seach et al., 2010; Taylor-Robinson et al., 2016), the possible protective effect of optimum infant feeding on allergic diseases and malnutrition remains controversial. The UK birth cohort showed that breastfeeding for ≥ 6 months and early introduction of complementary foods at ≤ 4 months was associated with an increased risk of eczema in children at 5 years of age (Taylor-Robinson et al., 2016), but no significant association was reported in the Melbourne HealthNuts study (Goldsmith et al., 2016). In terms of malnutrition, the Australian birth cohort showed that children who were introduced with complementary foods at ≤ 4 months were more likely to become overweight and obese between 10-11 years of age (Mannan, 2018). In contrast, Seach et al. (2010) found that delayed introduction of complementary foods was associated with lower risk of overweight and obesity in children at 10 years of age. Birth cohorts assessing the associations of infant feeding practices with allergic outcomes and malnutrition in developing countries is scarce (Budree et al., 2017; Caleyachetty et al., 2013; Gao et al., 2019). In addition, infant feeding factors associated with allergic outcomes and malnutrition that were previously identified in Western countries may vary in developing countries due to geographic and ethnicity differences. Therefore, more studies are needed to identify population-specific infant feeding practices for primary prevention of allergic diseases and malnutrition.

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 to identify their shared risk and protective factors which may be targeted for primary prevention. 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 and infant feeding practices with the 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 pregnant women during late pregnancy in Malaysia. Data on vitamin D status among Malaysian pregnant women is limited and the issue of vitamin D inadequacy in pregnancy is not targeted in the latest National Plan of Action for Nutrition of Malaysia III (NPANM III) (MOH, 2016a). 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, 2016a) 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 and feeding practices with the development of childhood allergy and malnutrition. Evidence from the present study can be served as a reference for policymakers and practitioners to provide evidence-based recommendations and update the current nutrition policies to improve maternal vitamin D status and infant feeding practices for prevention of allergic diseases and malnutrition in infants. The policymakers can make use of the evidence to develop nutrition education on vitamin D targeting the pregnant women, as well as to update the current infant feeding guidelines on common food allergens and management of possible allergic reactions when feeding the 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 during late pregnancy, compliance with WHO infant feeding recommendations, allergic diseases, and malnutrition in infants during the first year of life.

2 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.

3 To determine the interrelationships 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.

1.5 Alternative Hypotheses

H_a1: 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.

H_a2: 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 the pre- and post-natal environment in child's health and risk of diseases (Gluckman & Hanson, 2006). In the present study, allergic diseases and malnutrition, the two most common and earliest developing health issues in early childhood, were assessed as dependent variables. By referring to the DOHaD theory, the modifiable risk factors during the pre- and post-natal period that are linked to both allergic diseases and malnutrition were identified from the literature. Overall, findings from previous birth cohorts suggest that allergic diseases and malnutrition shared the similar risk and protective factors, namely, maternal vitamin D status and infant feeding practices (Blomberg et al., 2017; Eckhardt, Gernand, Roth, & Bodnar, 2015; Morales et al., 2015; Toko et al., 2016; Weisse et al., 2013).

Findings from several birth cohorts suggested that both lower and higher levels of maternal vitamin D levels were associated with the development of allergic diseases such as eczema and food allergy, as well as malnutrition in infants and young children (Blomberg et al., 2017; Eckhardt et al., 2015; Morales et al., 2015; Toko et al., 2016; Weisse et al., 2013). In terms of malnutrition, results from the birth cohorts demonstrated that infant feeding practices including breastfeeding duration, age at introduction of complementary feeding, and minimum dietary diversity were associated with the development of childhood allergic diseases and malnutrition, respectively (Gao et al., 2019; Lodge et al. 2015; Roduit et al., 2012; Udoh & Amodu, 2016; Vail et al., 2015; Woo et al., 2013). Based on the potential risk and protective factors identified from the literature, maternal vitamin D status and infant feeding practices including breastfeeding duration, age at introduction of complementary feeding, and minimum dietary diversity were assessed as independent variables in the present study.

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). The potential confounding factors for both allergic diseases and malnutrition were first identified from previous literature. In terms of allergic diseases, the potential confounding factors identified from

the literature include maternal age, ethnicity, educational level, work status, monthly household income, gestational age at blood withdrawal, parity, family history of allergic disease, gestational age at birth, child's sex, mode of delivery, birth weight, maternal and infant antibiotic use, pets at home, and daycare attendance (Nurmatov et al., 2012). While for malnutrition, the potential confounding factors identified from the literature include maternal age, ethnicity, educational level, work status, monthly household income, gestational age at blood withdrawal, parity, pre-pregnancy BMI, gestational weight gain, gestational age at birth, child's sex, mode of delivery, and birth weight (Hanieh et al., 2014, Mannan, 2018; Morales et al., 2015; Moschonis et al., 2017; Toko et al., 2016; Woo et al., 2013). For the allergic disease model, potential confounding factors significantly associated with allergic outcomes identified from univariable models and confounding factors based on conceptual justification as proposed by Nurmatov et al. (2012) were adjusted in the multivariable model. While for the malnutrition model, potential confounding factors significantly associated with malnutrition identified from the univariable models were adjusted in the multivariable model.

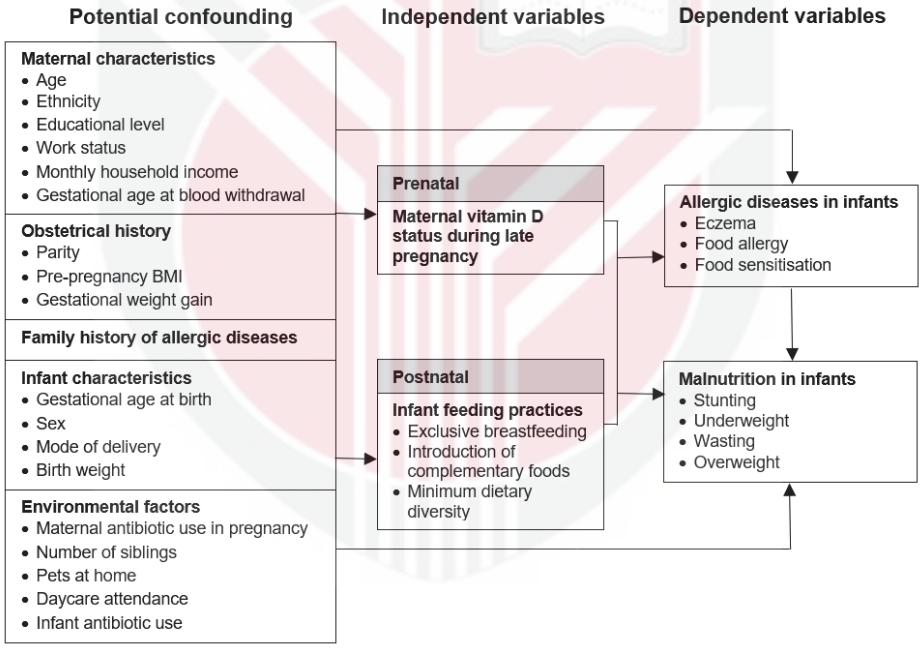

Figure 1.1: Conceptual framework

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