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Early Life Factors And Health Outcomes In Children And Mothers

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DEDICATION

To God – you are my everlasting strength and joy! To my wonderful boys, Fiyinfoluwa and Ayooluwa-you are one of the greatest reasons for my motivation. Your understanding of those many hours when mummy was busy trying to meet one deadline after the other will never be forgotten. Because of you, I could not give up even when I was overwhelmed. You gave me courage and motivated me to move on. Thank you from the bottom of my heart! I love you both very much!

To every mother, who never gave up on their dreams!

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ABSTRACT

This dissertation focused on early life exposures and their impact on children and mothers' health. It consists of three distinct studies with an overarching goal of understanding how early life factors influence health outcomes among children and mothers. The broad aims are: 1) to examine the association between maternal gestational weight gain and offspring weight at 1 year, while assessing the mediating role of birth weight; 2) to determine the association between breastfeeding practices and development of allergic conditions (eczema/skin allergy, hay fever/respiratory allergy, and asthma); and 3) to examine the association between breastfeeding and postpartum weight retention at 12 months.

The first study used recent data collected from a prospective cohort of Chinese pregnant women living in Daxin County, in southern China. Using multivariable linear regression models, we found that maternal gestational weight gain is positively related to offspring weight-for-age Z scores in early infancy and this relationship was significantly mediated by birth weight.

The last two studies utilized data from the Infant Feeding Practice Survey (IFPS) II, a longitudinal prospective cohort study of mothers and their newborn infants conducted by the CDC in 2005–2007. The second study combined data from IFPS II and its Year 6 Follow Up (Y6FU) collected in 2012. Using multivariable logistic regression models, we found that the odd of eczema/ skin allergy was higher among non-exclusively breastfed infants when compared with exclusively breastfed infants. However, no

association was found between breastfeeding practices and hay fever/ respiratory allergy and asthma.

The last study, which used multivariable linear regression models and generalized estimating equations found a significant association between breastfeeding (intensity and duration) and postpartum weight retention over time and at 12 months among a cohort of US mothers. When stratified by prepregnancy body mass index (BMI), this association remained significant only among normal weight women (BMI <25 kg/m^2).

In conclusion, early life exposures such as maternal gestational weight gain and breastfeeding practices were significantly related to health outcomes in children and mothers both in China and in the US. Targeted efforts should be made to encourage mothers to gain healthy weight in pregnancy and to adhere to the American Academy of Pediatrics recommendations for breastfeeding. Such efforts may be an effective strategy to improve health outcomes in the maternal and child health (MCH) population.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AAP .... American Academy of Pediatrics

BMI .... Body Mass Index

CDC .... Centers for Disease Control and Prevention

BF .... Breastfeeding

GWG .... Gestational Weight Gain

IFPS .... Infant Feeding Practice Survey

IOM .... Institute of Medicine

IQR .... Interquartile Range

MDG .... Millennium Development Goal

OR .... Odds Ratio

WAZ .... Weight-for-age Z-score

WLZ .... Weight-for-length Z-score

WHO .... World Health Organization

Y6FU .... Year 6 Follow-Up

CHAPTER 1

INTRODUCTION

Statement of the Problem

Mother's health and lifestyle behaviors are significant contributors to overall child's physical, developmental, immunological and psychological growth. Previous literature clearly indicates that early life exposures such as maternal gestational weight gain and nutrition have significant implications for both mothers and children's health outcome. [1,2] Suboptimal weight gain and related poor nutrition are important risk factors for both short- and long-term health complications. Reducing child mortality and improving maternal health with subsequent improvement in child health are listed as Goals 4 and 5 in the WHO Millennium Development Goals (MDGs). However, despite significant successes in reducing child mortality and morbidity, there are still huge disparities across different regions and countries, with the greatest gaps seen in developing countries. Childhood obesity now appears to be increasing worldwide with more developing countries seeing an increase in obesity rates.[3] Therefore, evidence on whether maternal factors such as gestational weight gain and nutrition are related to offspring and mother's weight is needed to be able to develop effective prevention and intervention strategies.

Childhood obesity remains a significant public health problem in the United States and worldwide with an estimated worldwide prevalence of 6.7%.[3] Recent findings also indicate that the Middle East, Pacific Islands, Southeast Asia, and China face the greatest threat of obesity.[3,4] The rise in obesity in developing countries is mainly due to ingestion of high-fat diet and increasing westernization. [3] The prevalence of overweight/obesity in China among children aged 2-18 years has almost tripled within 20 years with an estimated rate of 6.3 % in 1991 versus 17.1 % in 2001.[5] It is also important to note that an increase in obesity is seen in both rural and urban areas in China. [6] Aside from the short- and long-term complications of childhood obesity, the economic burden of managing obesity and its consequences are also high with an estimated cost of $147 billion in the United States in 2008.[7] Health care expenditures for managing obesity and its related complications are predicted to continue to rise. [8,9] Globally, it was estimated that obesity accounts for between 0.7% and 2.8% of a country's total healthcare expenditure.[10]

Maternal gestational weight gain (GWG) which is defined as the amount of weight gained by a pregnant woman between the time of conception and time of labor, [11] has been shown to be associated with the risk of overweight in offspring.[12-14] On the other hand, inadequate maternal weight gain is also an important risk factor for low birth weight and small for gestational age baby (SGA).[15] It has been proposed that intrauterine exposure to a suboptimal nutritional environment such as excessive gestational weight may lead to fetal pancreatic β cells dysfunction and subsequent insulin metabolism dysregulation and predisposition to obesity and metabolic disorder later in life.[16,17] Despite this biologic mechanism, the association between GWG and childhood obesity, is not totally clear and is less studied in developing countries. Understanding risk factors predisposing to childhood obesity may lead to the development of effective intervention strategies which may subsequently reduce obesity in adulthood and decrease healthcare expenditure.

Another significant predictor of a good health outcome in infancy is proper feeding and nutrition. The WHO global recommendation on infant feeding states that infants should be exclusively breastfed for the first six months of life for optimal growth and development.[18] Breastfeeding has been established to be the best source of infant feeding in the first six months of life if there are no contraindications. In 2012, the American Academy of Pediatrics emphasized its previous recommendation of exclusive breastfeeding for about six months, followed by continued breastfeeding for 12 months or longer as mutually desired by mother and infant and introducing complementary foods.[19] Many benefits of breastfeeding on health outcomes of children have been well documented in most developed countries.[20,21] However, its role in reducing or preventing the incidence of allergies is controversial with some studies showing positive effects and some showing negative or no association.[22-26] The incidence of allergies has been on the increase in the United States and worldwide, [27] but it is not clear how breastfeeding decreases the risk of skin, respiratory and other allergies during early childhood. More importantly, unlike other benefits of breastfeeding, the link between breastfeeding and allergic conditions is less well established, and results have been mixed. Apart from its content of carbohydrates, fat, and proteins, breast milk is also known to contain immunoglobulins and other immunocompetent cells which may confer long-term protection against allergies.[23,28] Establishing a causal association between breastfeeding and development of allergies may help public health practitioners propose evidence–based intervention to improve infant's health. It may be helpful to know if breastfeeding protects against allergy in infancy and if its protective effect persists till early childhood.

Breastfeeding is also known to provide health benefits for mothers including reduced risk of hypertension, and breast and ovarian cancers. [29,30] However, its role in reducing postpartum weight is less established and results have been mixed.[31,32] Studies have shown that postpartum weight retention can lead to increased risk for overweight and obesity in women, which is ultimately associated with poor health outcomes including cardiometabolic disorders[33-35] and increased risk of cancers.[36] Recent estimates show that 37% of reproductive age women (20-39 years old) are obese.[37]

While lifestyle and sociodemographic factors have been shown to play a significant role in weight gain among women, it has also been proposed that prolonged breastfeeding improves fat mobilization and glucose homeostasis and increases energy expenditure which may reduce postpartum weight.[38] Understanding modifiable risk factors predisposing to adverse health outcomes is necessary to implement effective intervention strategies to prevent morbidity and reduce mortality from obesity among women.

Because of the limited numbers of well-designed studies in the above-mentioned areas, the central theme of this dissertation aimed at exploring early life exposures influencing health outcomes in both mothers and children. The knowledge derived from these studies may be useful in reducing morbidity and mortality and improving overall health outcomes in the MCH population both in the US and developing countries.

Scope of Study

This dissertation is focused on examining early life factors influencing health outcome in mothers and children using data from China and the US. The first study examined the association of GWG on offspring weight at 1 year while assessing the specific role of birth weight as a mediator. In this study, we were interested in: 1) examining the correlates of GWG, 2) examining the association of GWG on offspring weight at 1 year, and 3) examining the specific role of birth weight as a mediator in the association between GWG and offspring weight at 1 year. The second study examined the association between breastfeeding (BF) and allergic conditions in early childhood. Specifically, we assessed duration and exclusivity of breastfeeding and its association with allergic conditions and asthma among 6-year-old US children. Lastly, we examined the association between BF practices and allergic conditions which included 1) eczema /skin allergy, 2) hay fever/respiratory allergy, and 3) asthma among 6-year-old US children. The third objective of this dissertation was to determine the association between breastfeeding intensity and duration on postpartum weight retention at 12 months. We also examined the longitudinal relationship between breastfeeding and postpartum weight retention over time at 6, 9, and 12 months.

Specifics Aims and Research Questions:

Specific Aim 1: Determine the association between maternal gestational weight gain and offspring weight at 1 year in rural China, while assessing the mediating role of birth weight in this relationship

- Research Question (RQ) 1.1: What are the correlates of maternal GWG in rural China?

- RQ 1.2: Are total GWG and adequacy of GWG associated with offspring's weight at age 1 in rural China?
- RQ 1.3: Is the relationship between GWG and offspring weight mediated by birth weight? If yes, what is the proportion mediated by birth weight?

Specific Aim 2: Determine the association between breastfeeding practices and allergic conditions and asthma among 6-year-old US children.

- RQ 2.1: What are the correlates of exclusive breastfeeding duration among US mothers?
- RQ 2.2: Do breastfeeding practices (exclusive breastfeeding and duration of breastfeeding) influence the prevalence of allergic conditions and childhood asthma?
- RQ 2.3: Are there any protective effect of breastfeeding practices on allergies among high-risk children (children with family history of allergy and infantile history of eczema)?

Specific Aim 3: Determine the association between breastfeeding practices and postpartum weight at 12 months among a cohort of US mothers.

- RQ 3.1: What is the prevalence of high breastfeeding intensity (defined as the number of milk feedings that are breastmilk) among US mothers?
- RQ 3.2: Does high breastfeeding intensity or duration reduce mother's risk for postpartum weight retention?
- RQ 3.3: Is this relationship modified by mother's prepregnancy BMI?

Significance of Dissertation

Study 1: Recent literature has shown that maternal GWG is a significant factor influencing weight in offspring. However, few studies have examined this association in rural China. China has experienced drastic economic growth in the past two decades. Yet, there are significant disparities in health status by geographic region, urban/rural residence, ethnicity, sex, and socioeconomic status.[39] In addition, there is a paucity of studies conducted in rural China where health behaviors may be different when compared to women living in urban areas. Therefore, our study added to the body of knowledge in this field. Second, to the best of our knowledge, no study has assessed the mediating or moderating roles of birth weight in the relationship between GWG and offspring weight in infancy among Asian women. We are interested in evaluating the extent to which birth weight mediates the relationship between GWG and offspring's weight at 12 months. Understanding the role of birth weight as a mediating factor would help us determine both the direct and indirect effect of gestational weight gain on offspring's weight. The Daxin study cohort was chosen because the study was conducted in a rural geographic location in China, with the majority of residents being farmers and of low socioeconomic status.

Study 2: This study provided more information on the association between breastfeeding and distinct allergic conditions and asthma among a cohort of 6-year-old US children. With the increasing rates of allergic conditions and the economic burden of managing disease and its complication, this study helped to investigate other less-established benefits of breastfeeding. Our analysis provided results for distinct allergic conditions, and also assessed if breastfeeding reduced allergies among a high-risk group-defined as those with a family history of allergy, and history of infantile eczema. We also assessed reverse causation in the relationship between breastfeeding and allergic conditions. By assessing the role of exclusivity and duration of breastfeeding on allergic conditions in separate analyses, we showed specific associations between breastfeeding practices and prevalence of allergies.

Study 3: Obesity remains a significant public health problem in the United States, and rates are still high among reproductive age women. With low rates of exclusive breastfeeding in our study population, we assessed breastfeeding intensity, which was defined as the proportion of milk feedings that were breastmilk, and its association with postpartum weight. The use of data with repeated assessments of postpartum weight enabled us to conduct the longitudinal analysis. This study was not only useful in understanding the role of breastfeeding on mother's postpartum weight retention over time within a 1 year period, but findings may be useful to promote breastfeeding practice among US mothers.

Overall, the findings from this dissertation are not only useful for health planning and recommendations but may also be useful to improve maternal and child health locally, nationally, and globally.

CHAPTER 2

LITERATURE REVIEW

This chapter examined the literature related to the three major aims of this dissertation. I first reviewed existing literature on maternal GWG and offspring weight, IOM guidelines for GWG, and limitations of current GWG measures. Secondly, I reviewed the literature on breastfeeding practices and allergic conditions among children. Finally, I reviewed the literature on breastfeeding practices and mother's postpartum weight retention.

STUDY #1

Association between maternal GWG and offspring weight at 1 year in a Chinese population: assessing birth weight as a mediator or effect modifier

<u>Maternal gestational weight gain</u>

Maternal GWG is defined as the amount of weight gained by a pregnant woman between the time of conception and the time of labor which is usually secondary to many physiologic changes occurring in the body. It is well known that pregnancy represents a period of significant metabolic, hormonal, cardiovascular and respiratory challenges. It also represents a period of increased food intake and reduced physical activity. Due to these factors during pregnancy, there is a tendency for suboptimal weight gain which has implications for health outcomes for both mother and offspring. Some studies have shown positive associations between lifestyle behaviors (unhealthy diet/excessive nutrition, and lack of physical activity) and weight gain during pregnancy.[40-42] Both excessive and inadequate weight gain during pregnancy are risk factors for adverse health outcomes in infants. Inadequate gestational weight gain is associated with preterm birth and intrauterine growth restriction (IUGR) while macrosomia, shoulder dystocia, and childhood obesity are related to excessive gestational weight gain. [15,43-45]

Maternal GWG has been mainly attributed to fetal and placental growth, amniotic fluid accumulation, and expansion of maternal tissues such as mammary gland, adipose, blood, and uterus. [46,47] The revised guidelines for weight gain during pregnancy were published in 2009 by the Institute of Medicine (IOM) (Table 2.1). For normal weight women, the recommended weight gain during pregnancy is between 25-35 pounds. However, a recent review by Olson et al. showed that gaining more weight than recommended by IOM is far more common than gaining less weight, nearly at a ratio of 2:1.[48] In 2013, the estimated prevalence of excessive GWG was 47.5% in the US,[49] predisposing fetuses and infants to both perinatal and neonatal complications. The new recommendations for weight gain used the WHO body mass index (BMI)'s cut-off points to categorize pre-pregnancy weight, that is, underweight (<18.5), normal weight (18.5-24.9), overweight (25.0-29.9), and obese (≥30) (see Table 2.1). The recommendations have been supported by many studies with better health seen in women who gained weight within the recommended range and poorer health outcomes in women who did not.[50,51] Despite this, its use is still controversial among some racial groups especially Asian women because studies suggest that Asian women have a higher risk of diseases at lower BMI cut-off point such as ≥ 24.[52] The IOM's recommendation for GWG is the same for all pregnant women irrespective of race or ethnicity although its committee has called for more research to revise this approach.[46] However, BMI categories recommended for Asians are different from their Caucasian counterparts.[53]

Table 2.1. The 2009 IOM recommendations for total and rate of weight gain during pregnancy, by pre-pregnancy BMI

	Total weight gain	
	Range in kg	Range in lbs.
Underweight (<18.5)	12.5-18.0	28.0-40.0
Normal weight (18.5-24.9)	11.5-16.0	25.0-30.0
Overweight (25.0-29.9)	7.0-11.0	15.0-25.0
Obese (≥30.0)	5.0-9.0	11.0-20.0

Source: Weight Gain during Pregnancy: Reexamining the Guidelines, KM. Rasmussen and A.L Yaktine, Editors. 2009: Washington (DC)

GWG measurements

Various methods have been employed to measure GWG with the three most commonly-used methods being: 1) measuring total weight gain at delivery, 2) measuring weekly rate of weight gain in the 2nd and 3rd trimesters, and 3) measuring the adequacy of weight gain using the IOM guideline (excessive, adequate, and inadequate). For this study, we used all three measurements of GWG. However, each of them has its inherent bias and limitations. More importantly, they all appear to have a built-in correlation with gestational age at delivery.[54] First, total GWG defined as the total amount of weight gained from conception to delivery is correlated with duration of pregnancy because women who had earlier or preterm deliveries may not have had time to gain as much weight as termed deliveries or women who deliver at a later gestational age. [54] This indicates that gestational age at delivery influences the amount of weight gained, which may introduce bias to epidemiological studies exploring the influence of GWG on some gestational age-related outcomes such as preterm deliveries. Second, the average weekly rate of weight gain during the 2nd and 3rd trimester (i.e. total weight gain – expected 1st-trimester GWG) / (child's gestational age -13)), assumes that weight gain increases linearly as the pregnancy progresses. It has been established that there is minimal weight gain in the first trimester, with more rapid and linear growth in the last two trimesters.[55-58] As explained by Hutcheon et al., this measure of GWG has a positive correlation with gestational age at delivery and a pregnant woman who delivers at 28 weeks would have a lower average rate of GWG than if she delivers at 40 weeks.[54]

The third approach classifies pregnant women into three groups: inadequate, adequate, and excessive weight gain by evaluating the adequacy of weight gained based on the IOM guidelines.[59] This approach does not assume that weight gain is linear throughout pregnancy. However, it has its own limitations of assuming that women of normal prepregnancy BMI gain 2kg (i.e. 4.4lbs.) in the first trimester and may also be correlated with gestational duration, [54] which can potentially bias studies that are examining the effect of GWG on outcomes such as preterm birth and low birthweight. For example, if normal weight women gain more than 2kg in the first trimester, there will be a negative association between adequacy of weight gain and gestational age because the weight above 2kg is averaged over a shorter period for women delivering earlier or women with preterm birth.[54] This bias may be minimized if we examine a study population where almost all babies are delivered full-term.

GWG and offspring's weight

Childhood obesity remains a significant source of morbidity and mortality primarily due to short- and long-term health consequences including the risk of heart diseases, type 2 diabetes, respiratory diseases and adult obesity.[60,61] The estimated worldwide prevalence of childhood obesity is 6.7% with an estimated 42 million overweight or obese children under age 5.[4,62] This rapid increase in childhood obesity has also been observed in many developing areas such as Southeast Asia, China, and Pacific Islands.[3] Some studies have shown an association between maternal GWG and risk of overweight in offspring.[1,63,64] Despite this, the biologic mechanism explaining the association between GWG and offspring weight is not entirely clear. While genetic and behavioral factors of parents play a role, some studies have proposed that maternal nutrition regulates leptin metabolism which in turn influences the appetite regulatory system, adipocyte metabolism and subsequent risk of obesity in offspring.[65]

GWG and offspring's weight in China

The prevalence of overweight/obesity in China among children aged 2-18 years almost tripled within 20 years with an estimated rate of 6.3 % in 1991 versus 17.1 % in 2011.[5] Due to the rapid increase in socioeconomic growth and westernization, China has experienced a concurrent transitional increase in consumption of unhealthy foods and diets high in fats.[5, 6] China is the 2nd largest world economy and is still growing. However, despite improved economic growth, health disparities in maternal and child health in China are large.

Although many studies were conducted to understand the association between GWG and childhood obesity among women living in developed countries such as the United States and the United Kingdom,[66-68] few studies have been done among Asian women and women living in developing countries. The paucity of studies in Asia, may be partly attributed to lack of scientific evidence for acceptable gestational weight gain among Asian women.[15,69] In addition, inadequate GWG or lack of healthy nutrition was a much greater concern in early studies. However, increased intake of unhealthy food and sedentary lifestyles have become more prevalent in the last few decades as a side effect of economic growth, thereby justifying the need for more studies in this area. Of the few studies that have been conducted to assess the relationship between excessive GWG and offspring weight among Chinese women, a positive association has been found. [12,13,15] For example, one of the studies conducted in Tianjin city found that the adjusted odds ratio (OR) for overweight (OR:1.29; 95% CI: 1.23-1.36) or obesity (OR:1.31; 95% CI: 1.23-1.40) at 12 months old was significantly higher among infants born to mothers with excessive GWG compared with infants born to mothers with adequate GWG.[43] Another study conducted in 27 cities and counties in China found that weight gain above the IOM recommendation was associated with a higher risk of macrosomic (OR 2.0, 95 % CI 1.9–2.1), and large for gestional age (LGA) babies (OR 1.9, 95 % CI 1.8–1.9) when compared to women who gained within IOM recommendation.[12] In addition, it is important to note that several published studies on gestational weight gain in China were all conducted in big cities.[12,15,43,44,70] We do not know whether gestational weight gain status in rural areas are similar to those found in the urban areas and whether the association of GWG and offspring weight persists in rural areas. Recently, there appears to be a differential trend in obesity prevalence according to the region, urban/rural residence, and socioeconomic status (SES) with more increase seen among people living in rural areas and people with lower SES status.[6]

The specific role of birth weight is critical when assessing the relationship between GWG and offspring weight in infancy. It is not clear if birth weight mediates this relationship or simply acts as a confounder in this relationship. Although many studies have shown a positive correlation with GWG and birth weight, it is possible that the impact of GWG on offspring's weight is through its indirect effect via birth weight. Simply adjusting for birth weight as a potential confounder cannot explain the indirect effect of GWG via birth weight.

Due to the rapid increase in overweight and obesity among children in China, and the high prevalence of excessive GWG in urban China,[43,71,72] rigorous scientific research is essential to understanding the association between maternal GWG and offspring weight in rural China. Using the IOM recommendations for GWG, the objective of study 1 was to determine the association between maternal gestational weight gain and offspring weight at 1 year old among a cohort of Chinese pregnant women while assessing the specific role of birth weight as a mediator in this association.

Study #2

Association between breastfeeding and development of allergic conditions (eczema/skin allergy, hay fever/ respiratory allergy) and asthma

Introduction:

Based on scientific evidence confirming the benefits of breastfeeding, the World Health Organization (WHO) recommends exclusive breastfeeding for the first six months of life, after which other foods are introduced in combination with continued breastfeeding till two years of age.[18] There have been significant strides in global awareness of the importance of breastfeeding. The role of breastfeeding in reducing childhood diseases and infection has been well established[73],[21,74], but its role in reducing the incidence of allergies is less established and still controversial.

Contents of breast milk

Human breast milk is known to undergo three stages of lactation, which includes colostrum, transitional, and mature milk. Colostrum, which is secreted in the first few days postpartum, is known to contain many factors such as IgA, leucocytes, lactoferrin, and growth factors. Transitional milk which is similar in contents as colostrum, typically starts from 5 days to two weeks postpartum, after which mature milk begins between 2-6 weeks postpartum. [75,76] Breast milk contains many macronutrients (protein, fat, lactose and energy), micronutrients (vitamins and iodine), immunological factors (immunoglobulins (Ig) A, G, and M, lymphocytes, T cells), and growth factors and has been shown to provide many short- and long–term benefits including neurological and physical development. [77] The bioactive components such as secretory IgA and IgG in breast milk confer passive immunity while other factors such as T-cells actively stimulate the immune system to fight against infection.[77-79]

Benefits of breastfeeding

Many studies have established the importance of adequate nutrition during infancy and breastfeeding, and human milk is the acceptable standard for infant feeding. Well-documented benefits of breastmilk include increased resistance to disease and infection, reduction in episodes of respiratory infections, gastrointestinal disease, otitis media, Sudden Infant Death Syndrome (SIDS), and reduced risk of both type 1 and type 2 diabetes mellitus. [21,73,74,80-83]

Epidemiology of Allergic Conditions in Infancy

Allergic conditions are common diseases and remain a significant cause of morbidity in early childhood. Allergies occur when the immune system reacts abnormally to a foreign substance such as pollen, bee stings, peanuts that usually would not produce such reaction in most people. According to the American Academy of Allergy Asthma and Immunology, allergic conditions which include allergic rhinitis, hay fever, eczema, atopic dermatitis, asthma, and food allergy have experienced a dramatic increase worldwide particularly in westernized countries.[27,84] The estimated prevalence of sensitization to one or more common allergens is about 40-50% worldwide, [27] and allergic rhinitis is estimated to affect 10 to 30% of the population globally. In 2012, approximately, 13% of US children aged 5-11 years have a skin allergy, and 12.1% of children reported respiratory allergies in the past 12 months. [85]

In addition to contributing to morbidity and many school absences, allergic conditions also have significant economic implications. In the United States, the total estimated cost of asthma has risen from $10.7 billion in 1994 to $62.8 billion in 2009.[86] Globally, the economic burden of asthma and other allergic conditions is also rising. [87,88]

Relationship between breastfeeding and allergies

Because of the presence of immunoglobulins in breast milk, one assumes that it would confer immunity against allergic diseases. Breast milk is immunologically complex containing factors that may protect against food allergens (IL-4, IL-5, IL-13, IL-8) as well as may induce food allergens (TGF-β, soluble CD14, spermine, α-linoleic acid), which may partially explain why epidemiological studies have been inconsistent.[89]

There remains a gap in knowledge on how breastfeeding methods (exclusive versus non-exclusive) and duration relate to allergies in children. It is not clear how categories of breastfeeding such as ever versus never breastfeeding, breastfeeding duration >4-6 months or exclusive versus non-exclusive breastfeeding influence prevalence of common allergies. Results from studies have been mixed with some showing positive associations and others showing negative or no associations.[22-26] A prospective cohort study which followed up infants during their first year and then at ages 1, 3, 5, 10, and 17 years showed that the prevalence of atopy during follow-up was highest among infants who were breastfeeding while the prevalence of eczema at ages 1 and 3 was lowest among infants who had longer duration of breastfeeding ($P<0.05$). However, these infants were born during the first three months of the year in Finland with ages range between 1-4 months at their first pollen exposure, and this may have attributed to the high prevalence of respiratory allergies (20%) seen in this cohort.[23] A recent review and meta-analysis found a protective effect of ever breastfeeding on asthma from 5-18 years when compared to never breastfeeding, but no significant association was found between exclusive breastfeeding greater than 3-4 months and asthma at 5-18 years. Also, there was no significant association between more versus less duration of breastfeeding (3-4 months) on food allergy. However, the study did find reduced risk of eczema below the age of 2 years when comparing exclusive breastfeeding greater than 3-4 months with other types of feeding, but no association was found when comparing more versus less duration of breastfeeding. Moreover, a reduced risk of allergic rhinitis was found only below the age of 5 years when comparing more versus less duration of breastfeeding (OR:0.79 (0.63,0.98).[22] However, this meta-analysis may have been impacted by between-study heterogeneity secondary to the length of recall of breastfeeding. As explained by the authors, recall bias results from mothers with allergic children who made a conscious decision to breastfeed longer and therefore may recall a longer breastfeeding duration than mothers who did not have allergic children.

Despite findings from other systematic reviews of a somewhat protective effect on breastfeeding on allergic conditions, results may have been impacted by methodological concerns due to lack of compliance with standards for performing systematic reviews and not addressing heterogeneity between studies.[90] Other concerns when comparing studies that have examined the role of breastfeeding in the prevalence of allergic conditions include methodological difference such as retrospective versus prospective studies and study design flaws such as lack of information on duration of breastfeeding, extent of breastfeeding exposure (exclusive versus non-exclusive), lack of specific case definition of each type of allergic condition, small sample size, lack of subgroup analysis, and not considering the age period (infancy, early childhood, adolescence). We addressed some of the above-mentioned limitations by using a large sample size with extensive data on US mothers and their offspring. To this end, the primary objective of the second study is to determine the association between breastfeeding (BF) and common allergic conditions using data from IFPS II and its Y6FU. Specifically, we assessed methods of breastfeeding i.e. exclusive vs. non-exclusive and duration of breastfeeding in this cohort of US mothers and their offspring. Lastly, we examined the association between BF and allergic conditions which include 1) eczema /skin allergy 2) hay fever/respiratory allergy, and 3) asthma at six years old while accounting for eczema history during infancy. A better understanding of breastfeeding on prevalence of allergies in school-age children may be useful to propose early intervention programs

Study #3

The association between breastfeeding practices and postpartum weight retention among a cohort of US mothers

Obesity remains a major public health problem both in the US and worldwide with an estimated prevalence of 37% among reproductive-aged women (20-39 years).[37] Pregnancy and weight gain during pregnancy appear to be a major contributing factor to obesity rates among women [91]with subsequent predisposition to other chronic diseases such as heart disease, type 2 diabetes, and stroke. On average, it has been estimated that women retain between 0.5 to 3kg of weight gained during pregnancy, [92] however, a modest proportion (14-20%) retained > 5 kg more than their prepregnancy weight at 6-18 months postpartum.[93-95]

Although, many studies have shown health benefits of breastfeeding for both mothers and their offspring, the association between breastfeeding and postpartum weight retention is less clear, and results have been mixed. [31,32] While other factors such as lifestyle behavior, socioeconomic status, parity, gestational weight gain are predisposing factors to postpartum weight retention, breastfeeding is also assumed to reduce postpartum weight retention due to the energy expenditure associated with lactation. However, systematic reviews examining this association have shown mixed results. [91,96] Therefore, it is relevant to study this relationship among a cohort with multiple assessments of breastfeeding.

The relationship between breastfeeding and postpartum weight retention

The majority of studies examining the relationship between breastfeeding and postpartum weight change are mostly observational studies (prospective and retrospective) [91,97-105]. Most of the prospective studies revealed no significant association between breastfeeding and postpartum weight retention,[99,103,104] while others showed an association. [97,105,106]. Studies vary in terms of confounding variables adjusted for. However, the majority of studies which showed significant associations, adjusted for gestational weight gain[102,106] and prepregnancy weight, [97,105,106] and parity. [105]

Reviewed studies had objective assessments of postpartum weight, and time of weight assessment ranged between 1-3 months and > 6 months postpartum, while some assessed weight via mother's self-report. Some studies found covariates such as GWG, parity, age, parity and prepregnancy BMI, and lifestyle factors as important factors predisposing to postpartum weight retention. A systematic review by Neville et. al. identified heterogeneity among studies examining this association ranging from the definition of breastfeeding, sample size, and duration of follow-up, methods of postpartum weight assessments, and failure to adjust for key covariates including prepregnancy BMI, gestational weight gain, and parity. Another issue raised is bias related to the selection of women into studies reviewed, with the majority of studies conducted among high socioeconomic status and educated women. Thirdly, there was also heterogeneity in statistical analysis, and some studies did not consider repeated measurements of weight change at different time points. [91]

Various biologic mechanisms underlying the impact of breastfeeding on maternal metabolism and postpartum weight have been proposed, and this includes beneficial effects of lactation such as decrease in blood lipids, increase in fat stores mobilization, and increase in insulin sensitivity. [38,107,108] Secondly, lactation also increases energy expenditure by 15%-25%, [38,109] and mothers who breastfeed exclusively also need an additional caloric energy for milk production which is assumed to aid weight loss during the postpartum period. Lastly, some studies have suggested that lactation alters body composition by promoting weight loss due to increased energy expenditure and regional fat distribution from the trunk and thigh.[108,110] Despite these biologic mechanisms, results from studies have been mixed.

The purpose of this study was to examine the relationship between breastfeeding and postpartum weight retention among a cohort of US women. Understanding correlates of breastfeeding and how this influences postpartum weight change may help us proffer evidence-based solutions to improve obesity rates among women.

CHAPTER 3

METHODS

Data Sources

With the goal of examining early life factors on child health outcomes for developing countries and in the US, we utilized two datasets. The first aim was analyzed using data from the Daxin study which was conducted in a cohort of Chinese postpartum women. The second and third aims were analyzed using the Infant Feeding Practice Survey (IFPS) II conducted among US mothers and their offspring in 2005 -2007 and its year 6 follow-up (Y6FU) study.

Data Source for Aim 1- The Daxin Study

The Daxin Study is a recent prospective cohort study conducted between 2013 and 2015 in Daxin County, Guangxi Zhuang Autonomous Region in southern China. Daxin County, a border county adjacent to Vietnam (see Figure 3.1), has a population of 359,800 people with over 90% of them being rural and minority population (Zhuang and Yao minorities). Daxin County is a rural area which is well known for its focus on agriculture with its main crops being rice, corn, sugarcane and soybean, and mining industry, and tourism. The Daxin study was originally designed to assess the impact of maternal methylmercury from rice ingestion on offspring's neurodevelopment.

Figure 3.1 Map of Guangxi Zhuang Autonomous Region and Daxin County

Study Design and Population

Maternal-offspring dyads recruitment occurred at parturition and was limited to women who gave birth in the hospital. Women were eligible to be enrolled in the study if they were in good general health, married, lived in Daxin County for the next 12 months, have no plan to change their residency while pregnant, and have no preexisting chronic medical conditions. Mothers were recruited from 2013 -2014 and followed up with their 12-month-old offspring from 2014 -2015. A total of 1,261 women gave birth in the hospital in the year 2013 and 2014. After excluding 228 (18%) who were ineligible due to infectious disease (e.g., Hepatitis B), 574 (46%) who were ineligible because they resided outside Daxin County, and 51 eligible mothers who refused participation (4.0%), 408 (32%) mothers who were eligible provided informed consent. However, 10 mothers were subsequently excluded because they did not give birth in the hospital (n=1), were ineligible due to residency status (n=3), gave birth to twins (n=1), did not complete data collection (n=5), resulting in a cohort of 398 mothers. Among these women, 318 completed the follow–up visit at 12-14 months, thus the follow-up rate was approximately 80%. See Flow Diagram in Chapter 4 (Figure 4.1)

During their hospital stay, women completed a questionnaire which has information on our exposures of interest such as maternal BMI and gestational weight gain. Data were also collected on other maternal characteristics such as socio-demographic characteristics, lifestyle behaviors, family history, occupational history, and household information. All women and their offspring were followed up once between 12-14 months after delivery. Information such as breastfeeding history, household information, parental knowledge, etc. was also obtained at the follow-up visit. In addition, anthropometric measurements of offspring were obtained at birth and at 1-year follow-up visit by research staff at the hospital. Neonatal anthropometry was collected from neonatal medical charts. Approval for the study was provided by the University of South Carolina Institutional Review Board, and the Xinhua Hospital Ethics Committee (Shanghai, China).

Study 1: Maternal GWG and offspring weight in early infancy

Purpose

Aim 1: 1) To determine correlates of maternal GWG in rural China 2) to determine the association between maternal gestational weight gain and offspring weight at 1 year in a Chinese population, and 3) to examine the mediating role of birth weight in the association between GWG and offspring weight.

Study design

A prospective cohort study design.

Study variables

The main exposure of interest was maternal GWG assessed both as a continuous variable and a categorical variable. Anthropometric measurements such as height and prenatal weight were obtained from medical charts. In addition, research staff measured weight at delivery and reviewed medical charts if there were discrepancies. Prepregnancy body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Participants were categorized using the IOM's guidelines for GWG and the Chinese BMI cut-off points: underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5-23.9 kg/m^2), overweight (BMI 24-27.9 kg/m^2), and obese (BMI ≥ 28 kg/m^2). Two methods of GWG calculation were used 1) total GWG (kg) at delivery defined as the difference between pre-pregnancy body weight and weight at delivery and 2) measuring the adequacy of weight gain. Total GWG was analyzed as a continuous variable, while adequacy of weight gain was analyzed as a categorical variable using the 2009 IOM classification and the Chinese BMI cut-off points.[46,111] Adequacy of weight gain was defined as 12.5–18 kg, 11.5–16 kg, 7–11.5 kg, and 5–9 kg for underweight, normal weight, overweight, and obese women, respectively. Chinese BMI cut-off points were used to categorize a woman's prepregnancy BMI as underweight (< 18.5 kg/m^2), normal weight (18.5-23.9 kg/m^2), overweight (24-27.9 kg/m^2) , and obese (≥ 28 kg/m^2).[112] Based on IOM classification, weight gain was categorized as inadequate, adequate, and excessive weight gain if weight gain is below, appropriate, or above the recommendations,

Outcomes: Offspring weight-for-age Z-scores (WAZ), weight-for-length Z-scores (WLZ)

The main outcomes of interest were weight-for-age and weight-for-length Z scores. Infants' anthropometric measures such as weight and length at 12 months were assessed by trained research staff. Using WHO growth standards and SAS macros, percentiles and Z-scores for weight-for-age and weight-for-length were calculated while accounting for child's sex.[113]

Covariates assessment

The mediating variable is birth weight. We used the INTERGROWTH-21st standards to calculate birth weight adjusted for gestational age Z scores. Based on current literature and data availability, variables such as maternal age, education, smoking, and ethnicity, and prepregnancy BMI, and offspring's sex were considered as potential confounders for the association between maternal GWG and offspring's weight. Maternal education in years was re-categorized as ≤ 6 years (elementary school); 7-9 years (junior middle school); 10-12 years (high school); ≥13 years (some college or more). Maternal smoke exposure was categorized as yes or no, while prepregnancy BMI was categorized as underweight (<18.5 kg/m^2), normal weight (≥ 18.5 and ≤ 23.9 kg/m^2), overweight (>=24.0 and ≤ 27.9 kg/m^2), and obese (≥28.0 kg/m^2). Other categories are as follows: occupation (farmers or non-farmers), ethnicity (Zhuang and others).

Statistical analysis

All analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC). Descriptive statistics were conducted to assess the characteristics of both mothers and offspring according to the adequacy of GWG status. Continuous variables such as maternal age, BMI, gestational age, etc. were summarized using mean and standard deviation. ANOVA test was utilized to compare differences in continuous variables according to the adequacy of GWG status. The chi-square test or Fisher's exact test (for small samples) was used to summarize categorical variables such as smoking, education, income, occupation, child's sex, and ethnicity according to GWG status.

To evaluate the relationship between GWG and offspring weight, multiple linear regression models were utilized to compare the mean Z scores for weight-for-age, and weight-for-length at 12 months of age according to GWG.

Mediation analysis

It is important to assess the pathways linking GWG to offspring weight at 1 year. In epidemiologic studies, it is common to control for confounding or mediating variables by multivariate analysis. However, this approach may not be sufficient to identify the direct and indirect effect of exposure on the outcome. An alternative and useful approach is mediation analysis which can be described as a method in which a researcher explains the process or mechanism underlying how one variable affects the other variable.[114] According to McKinnon et al., a mediating variable is one that is in the causal sequence between two variables. The main purpose of mediating analysis is to assess 1) the total effect of the exposure on the outcome, 2) the indirect effect of the exposure on the outcome through one or a given set of mediating variables, and 3) direct effect of the exposure unexplained by mediators.[115] We propose using mediation analysis to evaluate the indirect and direct effects of GWG on offspring's weight with and without birth weight respectively. The pathway is shown in the figure below:

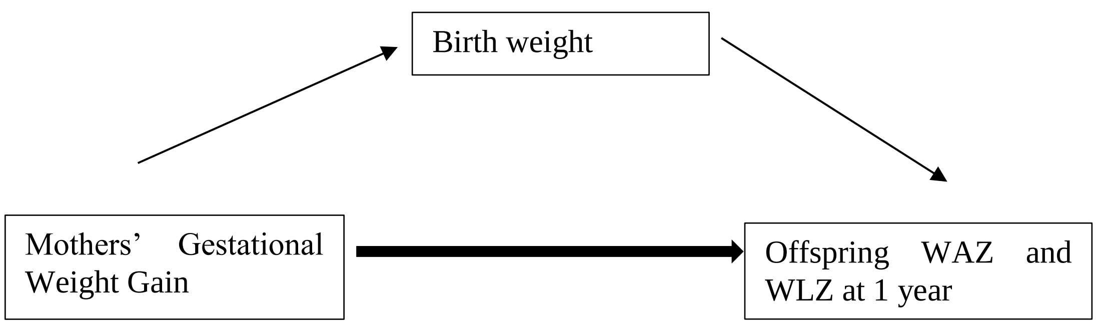

Figure 3.2. Mediation pathway between gestational weight gain and offspring weight

Traditional Approach to Mediation Analysis

A traditional approach of mediating analysis involves a comparison of two regression models in which one model adjusted for the mediator and the second model did not adjust for it. In this approach, the regression model adjusted for the mediator would be described as the indirect effect, while the model without adjusting for the mediator would be described as the total effect. Using my study variables as an example, the regression coefficient for the direct effect (from the adjusted model) represents the change in offspring weight for every unit change in GWG that is mediated by birth weight, while the regression coefficient for the total effect (from the unadjusted model) represents the change in offspring weight for every unit change in GWG. Finally, the indirect effect of the mediator (birthweight) can be estimated using the Judd and Kenny approach which subtracts the regression coefficient from 2 regression models below[116]:

Model 1: Offspring weight= $\beta_0 + \beta_1$GWG + β_2 (birth weight) + ϵ

Model 2: Offspring weight= $\beta_0 + \beta$GWG + ϵ

The indirect effect is $\beta_{indirect} = \beta - \beta_1$

This is called the *difference* method. The indirect effect can also be estimated by using the p*roduct* method which multiplies the coefficient of the path from exposure to the mediator and the coefficient of the path from mediator to the outcome.[117] After the coefficient of the indirect effect has been generated, its significance is assessed by using the bootstrapping method developed by Shout and Broger. [118]

According to Baron and Kenny 1986 [117] and as described in the Valeri and Vanderweele paper,[119] there are four criteria to be satisfied for a variable to be considered a mediator 1) a change in levels of the exposure variable significantly affects the changes in the mediator, 2) the mediator is significantly related to the outcome variable, 3) a change in levels of the exposure variable significantly affects the changes in the outcome, and 4) the association between the exposure and outcome variable is no longer significant when the mediators are appropriately controlled or included in the regression model. [117,119] However, the third and fourth criteria have been criticized by other researchers. For the third criterion the exposure needs not be significantly related to the outcome variable because when direct and mediated effects have opposite sign, the effect of exposure on the outcome may not be significant. Criterion 4 is also not required because mediation can be partial or complete. When complete, the path from exposure to the outcome would be zero, after controlling for a mediator. When incomplete, the path from exposure to outcome can still be significant, but the effect of exposure on the outcome would decrease if mediation is present. [119]

Counterfactual Approach to Mediation analysis

Recent evidence has shown that the traditional methods of mediation analysis tend to produce biased results due to incorrect statistical analysis and failure to consider the mediator-outcome confounding, exposure-mediator interaction, and mediator-outcome confounding affected by the exposure. Each of these limitations can generate biased estimates. Vanderweele et al. developed a SAS macro to address the limitations of the traditional approach. In addition, this method can offer p-values and % mediated. In epidemiologic studies, we collect confounders that will affect the exposure–outcome relationship but rarely do we pay attention to mediator-outcome confounders. Unmeasured mediator-outcome confounders can generate biased estimates of direct and indirect effects. It can also lead to collider bias illustrated in Figure 3.3. If we include M as a covariate and we did not adjust for mediator–outcome confounder which was unmeasured, we will induce a relationship between U and A.

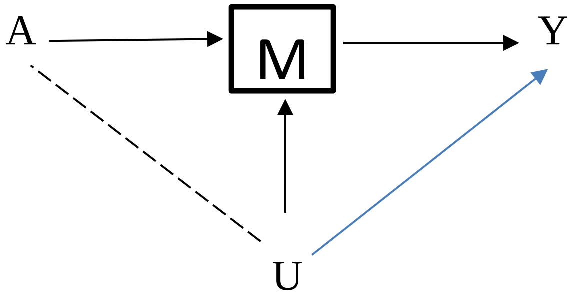

Figure 3.3: Effect of conditioning on a mediator M in the exposure (A)-outcome (Y) association in the presence of a mediator-outcome confounder (U)

To overcome the issues in traditional methods of Mediation analysis, VanderWeele et al. propose a counterfactual approach as a causal mediation analysis.

We defined some terms using the illustrations in the paper by Valeri et al.:[119]

Let **Y** denote some outcome of interest for each individual

Let **A** denote some exposure or treatment of interest for each individual

Let **M** denote some post-treatment intermediate(s) for each individual (potentially on the pathway between **A and Y**)

Let **C** denote a set of covariates for each individual

Let $\mathbf{Y_1}$ be the counterfactual outcome (or potential outcome) **Y** for each individual if **A** were set to 1

Let $\mathbf{Y_{1m}}$ be the counterfactual outcome **Y** for each individual if **A** were set to **1** and **M** to **m**

Let $\mathbf{M_1}$ be the counterfactual outcome **M** for each individual if **A** were set to **1**.

Using the terms mentioned above, we will determine the controlled direct effect, natural direct effect and natural indirect effect in the equations below:

a) Controlled direct effect (CDE): The average CDE comparing GWG level A=1 to A=0 setting birthweight =M i.e. CDE (m) = E [$Y_{1m} - Y_{0m}$]

b) Natural direct effect (NDE): The average NDE comparing GWG level A=1 to A=0 setting birthweight=M_0 i.e. NDE = E [$Y_1M_0 - Y_0M_0$]

c) Natural indirect effect (NIE): The average NIE comparing the effects of birthweight=M_1 versus birthweight=M_0 setting A=1 i.e. NIE = [$Y_1M_1 - Y_1M_{01}$]

Additional statistical details for Aim 1 are available in Chapter 4

Data source for Aims 2 and 3: The Infant Feeding Practice Survey II

The IFPS II survey was a consumer mail panel survey of US mothers and their newborn infants which was conducted by the CDC in 2005-2007. The longitudinal study focused on examining infant feeding practices throughout the first year of life and mothers' diet in their third trimester and at four months postpartum. It has extensive information on patterns of breastfeeding, formula feeding, complementary, and supplementary feeding. The study consisted initially of 4,902 women, but about 2,000 participants completed and returned questionnaire at 1 year follow up. The criteria for the postpartum follow-up study include the following: 1) mothers must be at least 18 years old at the time of prenatal questionnaire; 2) singleton and full or nearly full-term infants; 3) both mother and baby are healthy at birth; and 4) the infant does not have an illness or condition likely to affect feeding at birth or during their first year of life. Data were collected 12 times from mothers using a series of mailed questionnaires administered nearly monthly from the last trimester of pregnancy through the first year of infancy.[120,121] Apart from feeding practices, the questionnaire also had questions on allergic conditions and maternal sociodemographic characteristics, maternal diet, and health.

In 2012, eligible mothers who were enrolled between 2005-2007 were re-contacted to provide 6-year follow-up information for their child and themselves. The year 6 Follow-up (Y6FU) was a cross-sectional survey which provided follow-up data on the IFPS II cohort through a single questionnaire. This Y6FU collected extensive information on allergies and current health status, home environment, and food environment for the children at age 6. Participants qualified for the Year 6 follow-up (Y6FU) study if they completed the neonatal questionnaire and were not disqualified after the neonatal questionnaire. Participants were excluded if there was 1) infant death 2) diagnosis of a condition likely to affect feeding, and 3) mothers living in a geographic area without postal service because of the Gulf Coast Hurricanes in 2005. The total sample size of the Y6FU was 1542 children, which consists of about 52% of the original IFPS II cohort eligible for the follow-up study (n=2958).

In this dissertation, Study 2 used both IFPS II and Y6FU data while Study 3 utilized data from IFPS II alone. The Y6FU data was matched to the infant data from the IFPS II using sample ID.

Study #2: Breastfeeding and Allergic Conditions

Purpose

To determine the association between patterns of breastfeeding and allergic conditions (eczema/skin allergy, hay fever/respiratory allergy, asthma)

Study variables

<u>Exposure:</u> Breastfeeding practices

Breastfeeding information from the IFPS II data was obtained via self-administered questionnaire. Mothers were asked extensive questions on breastfeeding from neonatal period through 12 months including the following: 1) did you ever breastfed your child? 2) How old was your baby when you completely stopped breastfeeding and pumping milk? 3) In the past seven days, how often was your baby fed each food listed - breastmilk, formula, cow's milk, other milk, other dairy, soy, etc.? Exclusive breastfeeding duration was calculated as the midpoint of the infant age when the mother last reported feeding the infant only breast milk and the age when the mother first reported that she was not exclusively breastfeeding and children were categorized as 1) never breastfed 2) breastfed but not exclusively 3) exclusively breastfed $<$ 4 months 4) exclusively breastfed $\geq$ 4 months. Breastfeeding duration was categorized as 1) no breastfeeding, 2) breastfeeding duration $>$ 0 to 6 months, 3) breastfeeding duration 6 to 12 months, and 4) breastfeeding duration $\geq$12 months.

<u>Outcomes</u>: Allergic conditions at six-years old

The main dependent variables are self-reported physician diagnosed allergic conditions at six years old. These were obtained by asking mothers if a doctor or other health professional ever told them that their 6-year-olds have any of the itemized conditions: asthma, hay fever or respiratory allergy, eczema or any skin allergy. Based on this, our dependent variables which are physician-diagnosed asthma, eczema/skin allergy, hay fever/respiratory allergy conditions, which were each dichotomized as yes or no.

Covariates: Based on the literature [122,123]and data's availability, covariates such as child's sex, maternal smoking, race/ethnicity, socioeconomic status, maternal education, family history of allergy, and previous history of infantile eczema, were considered potential confounders. Additional details on methodology are provided in Chapter 5.

Statistical analysis

Baseline characteristics were described and compared according to exclusive breastfeeding duration using Chi-square tests for categorical variables and ANOVA tests for continuous variables. To evaluate the relationship between breastfeeding patterns and allergies, multivariable logistic regression models were utilized. Models were adjusted for race/ethnicity, income, pre-pregnancy BMI, education, offspring's sex, smoking, infantile eczema, and family history of atopy. Adjusted odds ratio and 95% confidence interval are reported. All analysis was conducted using SAS version 9.4 (SAS Institute, Inc.) For all outcomes, p-value < 0.05 is considered significant.

$$logit\,[\pi(x)] = \alpha + \beta 1 * breastfeeding + \beta 2 * gender + \beta 3 * maternal\ education + \beta 4 * race + \beta 5 * occupation + \beta 6 * infantile\ eczema \ldots$$

Additional details on the methodology for Aim 2 are provided in Chapter 5

Study #3: Breastfeeding and Postpartum Weight Retention

Purpose

To determine the association between breastfeeding intensity duration and postpartum weight retention among a cohort of US mothers.

Study Variables

Exposure: Breastfeeding intensity and duration

The main independent variables were 1) breastfeeding intensity which was defined as the proportion of milk feedings that were breast milk, and 2) breastfeeding duration. Breastfeeding information was obtained via 10 postpartum self-reported survey questionnaires. Mothers were asked 1) did you ever breastfeed your child? 2) How old was your baby when you completely stopped breastfeeding and pumping milk? 3) In the past seven days, how often was your baby fed each food listed - breastmilk, formula, cow's milk, other milk, other dairy, soy etc.? Mothers were also asked to give an estimate of the average number of times they feed their infants with formula, and other types of milk including breast milk, cow milk, and other milk such as soy, rice, and goat milk. Breastfeeding intensity was calculated based on the collected information using this formula:

[Number of breastmilk feeding/ (breast milk + formula +cow's milk +other milk feedings)][124] We derived the mean breastfeeding intensity during the first 6 months of infancy if mothers completed 3 or more of the first 6 postpartum questionnaires. We categorized breastfeeding intensity into 1) high (if > 80% of milk feedings were breast milk, 2) medium (20-80% of milk feedings were breast milk), and 3) low (<20 % of milk feedings were breast milk). We also assessed breastfeeding duration 1) breastfeeding duration > 0 to < 3 months 2) breastfeeding duration 3 to < 6 months 3) breastfeeding duration 6 to < 9 months and 4) breastfeeding duration ≥ 9 months.

Outcomes: Postpartum weight retention at 6 and 12 months

Prepregnancy weight and postpartum weight over one year was assessed via mothers' self-report. Prepregnancy weight in pounds was assessed at the prenatal questionnaire. Also, at the 6, 9, and 12 months' postpartum questionnaire, mothers were asked how much they weighed in pounds. Postpartum weight retention at 6, 9, 12 months was calculated as the difference between mothers' self-reported weight at the corresponding month, and mothers' prepregnancy weight.

Covariates

Based on the literature, [2] known confounding variables were identified. They are: maternal age, maternal education (high school or less, some college, college graduate, and post-graduate), maternal race (Whites and non-Whites), poverty–income ratio (≤185%, 186%-300%, and >300%), marital status (married, unmarried), parity (nulliparous, multiparous), prepregnancy body mass index (BMI< 25 kg/m^2, 25 to < 30kg/m^2 , >= 30 kg/m^2), postpartum maternal smoking (yes and no), and meeting the 2009 Institute of Medicine guidelines for gestational weight gain (inadequate, adequate, or excessive).

Statistical analysis

Baseline maternal characteristics including maternal age, ethnicity, the education, prepregnancy BMI, occupation, smoking status, and poverty income ratio was described and compared according to breastfeeding intensity using Chi-Square tests for categorical variables and ANOVA test for continuous variables. Multivariate linear regression models were used to examine the association between breastfeeding intensity and weight retention at 12 months postpartum while adjusting for covariates. We also evaluated the association between duration of breastfeeding and weight retention. Based on previous studies that have shown that breastfeeding practices differ by prepregnancy BMI, we tested for interaction between breastfeeding intensity and prepregnancy BMI, and breastfeeding duration and prepregnancy BMI. Significance level for interaction was set at $p < 0.2$. We also examined the relationship between breastfeeding practices and repeated measurements of postpartum weight retention at 6, 9, and 12 months using generalized estimating equations (GEE) i.e. PROC GENMOD while specifying exchangeable variance structure. Statistical significance was set at $p < 0.05$ and all analyses were performed using SAS software (version 9.4; SAS Institute, Inc.

Additional details on the methodology for Aim 3 are provided in Chapter 6

$$PPWR = \beta 0 + \beta 1 * time + \beta 1 * Breastfeeding + \beta 2 * matenal\ education + \beta 3 * race + \beta 4 * poverty - income\ ratio + \beta 6\ parity\ \ldots$$

CHAPTER 4

MATERNAL GESTATIONAL WEIGHT GAIN AND OFFSPRING'S WEIGHT AT 1 YEAR OF AGE IN RURAL GUANGXI PROVINCE, CHINA: THE MEDIATING ROLE OF BIRTHWEIGHT

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ABSTRACT

Background: Little is known about the association between maternal gestational weight gain (GWG) and offspring's weight in developing countries especially in rural areas. We examined the association and assessed the possible mediating role of birthweight.

Methods: Data came from a prospective cohort study of 315 pregnant women and their offspring living in rural Guangxi province of China. GWG was examined as total weight gain and whether weight gain was excessive, adequate, or inadequate according to the Institute of Medicine's guidelines on weight gain. Mediation analyses were used to examine the total, direct, and indirect effects of GWG via birthweight on offspring's weight-for-age Z (WAZ) and weight-for-length Z (WLZ) scores at 12-14 months.

Results: Gaining inadequate weight during pregnancy (51.1%) was more prevalent than gaining excessive (20.0%) or adequate (29.8%) weight. In adjusted analysis, 1 kg increase in total GWG was positively associated with offspring's WAZ scores (β=0.02; p=0.044) but not with WLZ ((β=0.01; p=0.187). Thirty-two percent of the total effect of GWG on offspring WAZ was mediated by its indirect effect via birthweight, while 22% of the total effect of GWG on offspring's WLZ was mediated by birthweight. Gaining excessive or inadequate weight was not significantly associated with offspring's WAZ or WLZ scores in this cohort.

Conclusion: In rural China, maternal GWG was positively associated with offspring's WAZ scores at age one. Birthweight may mediate one-third of the association. Healthy weight gain during pregnancy may have an impact on offspring's physical growth in rural China.

INTRODUCTION

Childhood obesity has become a significant public health problem worldwide. Maternal gestational weight gain (GWG) defined as the amount of weight gained by a pregnant woman between the time of conception and the time of labor, is known to be associated with offspring weight.[11,125] Pregnancy represents a period of significant metabolic, hormonal, cardiovascular and respiratory challenges,[46] while it also represents a period of increased unhealthy food intake and reduced physical activity[126,127] which result in suboptimal weight gain and impacts both newborn and maternal health outcomes. Inadequate GWG is associated with preterm birth and intrauterine growth restriction, while excessive GWG is associated with macrosomia, shoulder dystocia, caesarean delivery, and childhood obesity.[15,43,44]

In 2009, the Institute of Medicine (IOM) published a revised guideline for weight gain during pregnancy. In the United States, however, gaining more gestational weight than recommended is far more common than gaining less weight, nearly at a ratio of 2:1 with the prevalence of excessive GWG estimated at 48% in 2015.[128] Maternal GWG varies across populations. In big cities (e.g. Tianjin, Wuhan) in China, for example, the prevalence of excessive GWG ranges between 38% and 57%, [43,71,72] but may differ in rural areas where food access is limited.

While an association between GWG and offspring's weight has been reported in developed countries,[46,129-131] little is known about maternal GWG and its association with offspring's weight in rural China. Of the few published studies conducted among Chinese women, the majority were conducted in big cities.[12,15,43,44,71] China has experienced strong economic growth and fast urbanization in the past two decades. Yet, the rural population still accounts for almost 60% of the Chinese population.[132] There are significant disparities in health status by geographic region, urban/rural residence, ethnicity, and socioeconomic status.[133] Compared to urban and Han majority residents in China, rural and minority residents (55 ethnic groups in China) are often of lower socioeconomic status, lack access to quality health care and preventive services, have poorer health behaviors, and have poorer health status.[132,133] As such, more maternal and child health research is needed in rural areas and among minority women in China.

Birthweight is positively correlated with GWG[134,135] and offspring weight in early childhood.[136] Intrauterine environment such as excessive maternal nutrition may play a significant role in the development of obesity in offspring.[137,138] Excessive GWG, an important marker of the nutritional environment,[125] is also related to increased birthweight in offspring. With increasing evidence of a U or J- shaped relationship between birthweight and obesity later in life,[139] it is possible that the impact of GWG on offspring's weight is mediated through birthweight. Simply adjusting for birthweight as a confounder is incorrect and would not explain the indirect effect of gestational weight via birthweight. To the best of our knowledge, no study has examined the mediating role of birthweight in the relationship between gestational weight gain and offspring weight in rural China. Therefore, this study examined the association between maternal GWG and offspring weight at 1 year while assessing the mediating role of birthweight in this association in a population-based prospective cohort of mother–child pairs living in rural China. Specifically, we assessed 1) the status of GWG and its correlates in this population, 2) the impact of GWG on offspring weight at 1 year, and 3) the possible mediating role of birthweight in the association between GWG and offspring weight at 1 year.

METHODS

Study Design and Population

Data came from a prospective cohort study conducted in Daxin county of Guangxi Province, China in 2013-2015. This study was originally designed to investigate the impact of maternal methyl mercury from rice ingestion on offspring's neurodevelopment.[140] Daxin has a population of 359,800 people including >85% Zhuang minority.

Maternal-offspring pair recruitment occurred at parturition and was limited to women who gave birth in the county Maternal and Child Health Hospital. Women were eligible for the study if they were in good general health, lived in the county during the previous three months, planned to remain in the county for the next 12 months, and did not have preexisting chronic medical conditions. A total of 1,261 women gave birth at the hospital during the period of 2013 and 2014. After excluding women who 1) had infectious diseases (mainly Hepatitis B) (n=228), 2) resided outside the county (n=574), and 3) refused to participate (n=51), a total of 408 eligible mothers provided informed consent and were recruited. Ten more mothers were subsequently excluded due to delivery outside the hospital (n=1), lack of residency status (n=3), giving birth to twins (n=1), or incomplete data collection (n=5), resulting in a cohort of 398 mothers. At 12-14-month follow-up visit, 80% (n=318) completed the visit (Figure 1). Approval for the study was provided by the University of South Carolina Institutional Review Board, and the XinHua Hospital Ethics Committee (Shanghai, China).

During their hospital stay, women completed a questionnaire, which included information on maternal socio-demographic characteristics, lifestyle behaviors, medical, familial, and occupational histories, and household information. Mother's anthropometric measurements such as height and prenatal weight were obtained from medical charts. Neonatal anthropometry was collected from neonatal medical charts at birth. At the 12–month follow-up visit, trained research staff obtained anthropometric measurements of offspring and collected information such as breastfeeding history and child's general health via questionnaire.

Gestational weight gain measures

Two measures of maternal GWG were developed. First, total weight gain at delivery was calculated as the difference between weight at delivery and pre-pregnancy weight. Second, we calculated adequacy of GWG using the Chinese prepregnancy body mass index (BMI) cut-off and the 2009 IOM GWG classification.[46,112] Adequacy of weight gain was defined as 12.5–18 kg, 11.5–16 kg, 7–11.5 kg, and 5–9 kg for underweight, normal weight, overweight, and obese women, respectively. Chinese BMI cut-off points were used to categorize a woman's prepregnancy BMI as underweight (< 18.5 kg/m^2), normal weight (18.5-23.9 kg/m^2), overweight (24-27.9 kg/m^2) , and obese (≥ 28 kg/m^2).[112] Based on IOM classification, weight gain was categorized as inadequate, adequate, and excessive weight gain if weight gain is below, appropriate, or above the recommendations, respectively.

Offspring's weight-for-age Z- scores and weight-for-length Z scores at 12 months

Offspring's weight at 12 months was assessed by weight-for-age (WAZ) and weight-for-length (WLZ) Z scores. Using the WHO growth standards, we obtained the percentiles and Z-scores for weight-for-age and weight-for-length taking into account child's sex and age.[113] The derived weight–for-age percentiles were used to categorize offspring further into underweight (<10th percentile), normal weight (10th to <85th percentile), and overweight (85th percentile). [113]

Covariates

First, birthweight was hypothesized as a potential mediating variable. Birthweight for gestational age Z-scores were calculated using the Intergrowth- 21 Newborn Birth standards, which were based on a reference population of 20,486 births from eight countries including 17% (n = 3551 births) from China. [141] Based on findings from previous literature, the following variables were considered as potential confounders: mother's age, education (<high school, high school, >high school, or university), prepregnancy BMI (kg/m^2), exposure to second-hand smoking (yes or no), occupation (farmers or non-farmers), ethnicity (Zhuang or other ethnicities), and pregnancy complications; and offspring's age at delivery in weeks and sex. Because of a small number of pregnancy complications in our sample (n=21), we categorized pregnancy complications into two groups (yes versus no complication).

Statistical analyses

Chi-square tests (Fishers exact, if small cell sizes) were used to describe categorical sample characteristics, while ANOVA tests were used to describe continuous sample characteristics according to categories of GWG groups. Generalized linear models were used to assess the relationship between GWG and WAZ and WLZ at 1 year of age. Regression models were adjusted for maternal age, prepregnancy BMI, gestational age, occupation, ethnicity, pregnancy complication, and child's sex. The inclusion of variables in our model was determined based on 1) literature review of known confounders and 2) if it changed the β coefficient by more than 10% when included in the model.

To determine the mediating role of birthweight, we used a SAS macro developed by Vanderweele et al.[119] We examined the total effect of GWG on offspring weight at 1 year, the indirect effect of GWG on offspring's weight measures through birthweight, and the direct effect of GWG unexplained by birthweight adjusting for maternal age, prepregnancy BMI, gestational age, maternal ethnicity, occupation, pregnancy complications, and offspring's sex. The interaction between GWG and birthweight z scores (mediator) was assessed. The proportion of effect mediated was calculated using this formula: (Natural indirect effect (NIE)/Total effect)*100.[142] All statistical analyses were conducted using SAS version 9.4 (SAS Institute Cary, NC). Statistical significance was set at p-values ≤ 0.05.

Sensitivity Analysis

Additional analyses were conducted by estimating the adequacy of GWG using the original BMI cut-off points in the 2009 IOM GWG recommendation, i.e., underweight (<18.5), normal weight (18.5-24.9), overweight (25-29.9), and obese (≥30). Furthermore, we estimated the adequacy of GWG using the WHO's BMI recommendations for Asians i.e. underweight (<18.5), normal weight (18.5-22.9), overweight (23-27.49), and obese (≥27.5).[143] Results of these analyses were compared with our initial analysis, which used the Chinese prepregnancy BMI cut-off.

RESULTS

Sample Characteristics

The mean age of mothers was 27.9 years (± 5.1). Mean total GWG and mean gestational age (GA) at delivery was 11.7 kg (±1.5) and 39.1 weeks (±1.2), respectively. According to the Chinese BMI cut-off points, 11.5% of mothers were overweight or obese prior to pregnancy, while 63.1% and 25.4% were normal weight and underweight, respectively. Majority of mothers were farmers (72.7%) and had less than high school education (81.3%). About 88% were of Zhuang ethnicity while 10% and 2% were of Han and other ethnicities, respectively. At 1 year of age, 23.2% of infants were below the 10th weight-for-age percentile according to the WHO growth standards. (Table 4.1)

GWG status and its correlates

Inadequate weight gain during pregnancy (51.1%) was more prevalent than gaining excessive (20%) or adequate (28.9%) weight based on the Institute of Medicine's guidelines for maternal GWG. GWG status was significantly associated with weight-for-age percentile at 1 year (p=0.007) and the mean birthweight of offspring born to mothers who gained excessive weight was significantly higher than that of mothers who gained inadequate and adequate weight (p=0.001). In this cohort, maternal education, occupation, ethnicity and pregnancy complication were not significantly associated with GWG status (p >0.05) (Table 4.1). Mothers of infants who were overweight at 1 year (> 85th percentile) had higher mean total GWG when compared to mothers of underweight or normal weight infant (14.4 kg versus 11.6 kg; p=0.009) (data not shown).

GWG and offspring weight at 1 year

In the crude analysis, there was a significant positive relationship between total GWG and offspring weight-for-age Z-scores (β=0.02; 95% CI: 0.01, 0.04; p=0.036). After adjusting for covariates, the association between total GWG and weight-for-age Z-scores remained statistically significant (β=0.02; 95% CI: 0.01, 0.04; p=0.044), i.e. for every 1 kg weight increase in GWG, offspring WAZ increased by 0.02. However, we did not find a significant association between WLZ and total GWG (β=0.01; 95% CI: -0.01, 0.03; p=0.187) (Table 4.2).

Mean offspring WAZ and WLZ were not significantly different among mothers with inadequate and excessive GWG when compared to adequate GWG (Table 3). However, the offspring of mothers with excessive weight gain had significantly higher WAZ compared with those of offspring of mothers with inadequate weight gain (β = 0.27; p=0.03) (Data not shown). No significant association was seen between the adequacy of GWG and infants' WLZ ($p>0.05$) (Table 4.3).

Mediating Role of Birth weight

After adjusting for confounders, birthweight Z-score was a significant mediator between total GWG and offspring WAZ. The natural indirect effect of GWG via birthweight was statistically significant (β=0.07; 95% CI: 0.01, 0.04; $p<0.01$). About 33% of the total effect of total GWG on WAZ was mediated via offspring's birth weight. Likewise, birthweight remained a significant mediator between categorical measures of GWG and offspring's WAZ at 1 year. When offspring of mothers with inadequate weight gain and excessive weight gain were compared with offspring of mothers with adequate weight gain, the natural indirect effect of GWG via birthweight was β= -0.11; 95% CI: -0.18, -0.03; p=0.004, and β=0.06; 95% CI: 0.02, 0.09; p=0.004, respectively. Approximately 48% of the effect of GWG on offspring WAZ at 1 year was mediated by birthweight when comparing offspring of mothers with inadequate weight gain to offspring of mothers with adequate weight gain. Results were similar when comparing WAZ of offspring born to mothers with excessive weight gain to offspring born to mothers with adequate weight gain (Table 4.4).

We also assessed the mediating role of birthweight in the association between GWG and offspring's WLZ. The natural indirect effects of total GWG and the adequacy of GWG via birthweight were statistically significant ($p < 0.05$). The proportion of the effect of GWG on WLZ mediated via birthweight Z-score was about 22%. However, the direct effect of both total GWG and adequacy of GWG on WAZ and WLZ were not significant (Table 4.4).

Sensitivity Analysis

When GWG was categorized using the WHO BMI cut-off points, women with inadequate weight gain had offspring with lower WAZ when compared with women with adequate weight gain (β = -0.23; 95% CI: -0.45, -0.02;p=0.041). Similar to initial findings, there was no significant difference in WAZ between offspring of mothers with excessive weight gain and offspring of mothers with adequate weight gain. Compared to adequate weight gain, inadequate GWG was also associated with lower WLZ at borderline significance (p <0. 1) (Supplementary table 1). When data were analyzed using the Asian prepregnancy BMI cut-off and IOM guidelines, offspring of mothers who gained inadequate weight had a lower WAZ compared to offspring of mothers who gained adequate weight at borderline significance (β = -0.21; 95% CI: -0.43, -0.01; p=0.053) (Supplementary Table 2).

COMMENTS

The present study assessed the relationship between maternal GWG and offspring weight at 12 months in a cohort of Chinese mothers and their offspring living in rural China. Results showed that total GWG was associated with higher offspring WAZ in early infancy. Our findings are similar to previous findings showing a positive relationship between maternal GWG and offspring weight.[43,144] However, we did not find a significant relationship between GWG and WLZ. Compared to the US (29%), the prevalence of inadequate GWG was much higher in this cohort (51%). In comparison to other studies conducted in Chinese cities,[43,71] the prevalence of excessive GWG in our study was lower (approximately 20%). The higher prevalence of inadequate GWG and lower prevalence of excessive GWG may be a reflection of lower socioeconomic status, [132,133]and poorer nutritional status in rural areas of China.[145] Despite this, the positive association between GWG and offspring weight in this cohort is of public health significance.

A recent study by Li et al. conducted in a big city (Tianjin) in China in a large sample (n=38,539), showed that about 40% of their participants gained excessive weight during pregnancy, and both prepregnancy BMI and maternal GWG were positively associated with higher risks of being overweight or obese in the first year of life.[43] Another study found that weight gain above the IOM recommendation was associated with two times higher risk of macrosomia and large-for-gestational-age (LGA) babies when compared to women who gained within IOM recommendation.[12]

Despite these findings, the biologic mechanism explaining the association between GWG and offspring weight is not totally clear. While genetic and behavioral factors of parents play a role, some studies have proposed that maternal nutrition regulates leptin metabolism which in turn influences the appetite regulatory system, adipocyte metabolism, and subsequent risk of obesity in offspring.[65] Other proposed mechanisms have linked GWG, which is partly due to an increase in adiposity, to subsequent insulin resistance in mid-pregnancy.[46] Insulin resistance increases the risk of impaired glucose tolerance, resulting in hyperglycemia in both mothers and fetuses.[46,146] Fetal hyperglycemia, which is a significant cause of fetal hyperinsulinemia, results in increased fetal adiposity and delivery of macrocosmic babies and a predisposition to childhood overweight.[46] Although we could not explore these suggested mechanisms, our findings suggest that higher total GWG is positively associated with offspring weight at 1 year.

A unique strength of this study is that we also assessed the mediating role of birthweight in the relationship between maternal GWG and offspring weight at 1 year. We found that birthweight adjusted for gestational age is a significant mediating variable in the association between GWG and offspring weight at 1 year of age. While the total effect and indirect effect via birthweight were significant, the direct effect of GWG was not statistically significant. It appears that the effect of GWG on offspring weight at 1 year is due to its indirect effect via birthweight. Our finding is consistent with another study which showed that almost half the effect of GWG on offspring BMI in adulthood was mediated through birthweight and childhood BMI. [131]

To be comparable with existing literature and also to best handle limitations of GWG measurements,[54] our study employed two common measurements of GWG: 1) total weight gain at delivery and 2) adequacy of weight gain according to IOM guidelines (excessive, adequate, and inadequate). As discussed by Hutcheon et al., these measures have a built-in correlation with gestational age at delivery.[54] First, total GWG is correlated with duration of pregnancy because women who had earlier or preterm deliveries may not have had time to gain as much weight as term deliveries or women who deliver at later gestational ages.[54] This indicates that gestational age at delivery will influence the amount of weight gained, which may introduce bias to epidemiological studies exploring the influence of GWG on some gestational age-related outcomes such as preterm deliveries. Our second measure, the adequacy of weight gained, is a categorical measure which classifies individuals into three groups: inadequate, adequate, and excessive weight gain based on the IOM guidelines. This approach does not assume weight gain is linear throughout pregnancy. However, it is limited by assuming that women gain a fixed amount of weight in the first trimester (i.e., 2kg for normal weight women), which may potentially bias studies that are examining the effect of GWG on outcomes such as preterm birth and low birthweight. In this present study, these biases are minimized because 95% of infants in this cohort were delivered at term (>37 weeks).

The present study has several strengths. The study used a recent (2013-2015) population-based prospective data which allowed us to establish temporal sequence between our exposure and outcome variables. Despite the relatively small sample size, the overall follow-up rate was 80%, which minimized selection bias secondary to loss to follow-up. The study population is also unique because the study was conducted in rural

China where many scientific studies in maternal and child health outcomes have not been explored. Therefore, our study is important to justify the need to develop lifestyle interventions that may help mitigate disparities in maternal and child health in this population. In addition, to the best of our knowledge, no study has assessed the mediating role of birthweight in the relationship between GWG and offspring weight in infancy among Asian women. Mediation analysis allowed the decomposition of the total effect of GWG into direct and indirect effect while estimating the proportion of effect mediated by birthweight.

The main limitation of our study is the relatively small sample size, which may have limited the ability to detect differences between groups. Also, despite adjusting for common, known confounders, there remains a possibility of residual confounding due to our inability to capture maternal lifestyle factors such as physical activity level and detailed information on infant diet in the first year. Finally, IOM guidelines for gestational weight gain are based on women in developed countries, and may not be appropriate for women in rural China.

In conclusion, maternal gestational weight gain is associated with offspring's weight in early infancy in rural China, and this relationship is possibly mediated via birth weight. Our result suggests that targeted nutrition programs should be designed to help pregnant women gain healthy weight and assist the healthy growth of infants in early infancy. Efforts should be made to help women gain healthy weight during pregnancy by paying attention to mothers' nutrition during pregnancy. Such programs will have profound effects on offspring's weight in addition to its beneficial impact on women's health.

Table 4.1. Sample characteristics of Study Participants According to Gestational Weight Gain Status

Variable	Total [a]	Gestational Weight Gain Categories (N=315)			P-value [b]
		Inadequate	Adequate	Excessive	
Total, No. (%)	315 (100.0)	161 (51.1)	91 (28.9)	63 (20.0)	
Age at delivery, mean (SE)	28.0 (0.3)	27.2 (0.5)	28.7 (0.5)	27.2 (0.7)	0.068
Prepregnancy BMI (kg/m^2), No. (%)					**0.003**
Underweight (<18.5)	80 (25.4)	46 (28.5)	23 (25.3)	11 (19.1)	
Normal (≥ 18.5 and ≤ 23.9)	199 (63.1)	108 (66.5)	55 (66.4)	36 (57.1)	
Overweight (≥24.0 and ≤ 27.9)	30 (9.6)	8 (5.1)	10 (11.0)	12 (19.1)	
Obese (≥28.0)	6 (1.9)	0 (0.0)	3 (3.3)	3 (4.8)	
Ethnicity, No. (%)					0.934
Zhuang	276 (87.6)	142 (88.2)	78 (85.7)	56 (88.9)	
Other ethnicities (Han +Others)	39 (12.4)	19 (11.8)	13 (14.3.)	7 (11.1)	
Occupation, No. (%)					0.252
Farmers	229 (73.9)	123 (77.4)	64 (72.7)	42 (66.7)	
Non-Farmers	81 (26.1)	36 (22.6)	24 (27.3)	21 (33.3)	
Education level, No. (%)					0.168
< High School	252 (81.3)	136 (85.0)	72 (80.0)	44 (72.1)	
High school	42 (13.6)	17 (10.6)	14 (15.6)	11 (18.0)	
>High school	16 (5.2)	7 (4.4)	3 (3.4)	6 (9.8)	

Second-hand smoking, No. (%)					0.095
Yes	128 (41.7)	58 (37.2)	37 (42.0)	33 (53.2)	
No	179 (58.3)	98 (62.8)	52 (58.0)	29 (46.8)	
Offspring sex, No. (%)					0.885
Male	157 (49.8)	80 (49.7)	47 (51.7)	30 (47.6)	
Female	158 (50.2)	81 (50.3)	44 (48.3)	33 (52.4	
Gestational age (weeks), mean (SE)	39.1 (1.2)	39.2 (1.1)	39.2 (1.2)	39.3 (1.3)	0.255
Birthweight (grams), mean (SE)	3117.9 (380.6)	3017.8 (363.6)	3189.3 (436.02)	3282.6 (356.6)	**0.001**
Total GWG (kg), mean (SE)	11.73 (5.1)	8.08(3.0)	13.31 (2.5)	18.70 (3.7)	**0.001**
Complication in pregnancy, No. (%)					0.646
Yes	20 (6.5)	11(7.0)	4 (4.5)	5 (7.9)	
No	290 (93.5)	147(93.0)	85 (95.5)	58 (92.1)	
Weight-for-age percentile at 1 year, No. (%)					**0.007**
<10th percentile	73 (23.2)	40 (24.8)	23 (25.3)	10 (15.8)	
10th – 85th percentile	230 (73.0)	120 (74.5)	60 (65.9)	50 (79.0)	
≥ 85th percentile	12 (3.8)	1 (0.6)	8 (8.8)	3 (4.8)	

[a] Frequency missing: Secondhand-smoking (n=8), education (n=5), occupation (n=5), pregnancy complication (n=5)
[b] Based on Chi-square test (fishers test for small samples) for categorical variables and ANOVA test for continuous variable

Table 4.2. Crude and adjusted analysis between total maternal gestational weight gain and weight-for-age Z-scores and weight-for-length Z scores

	Weight-for-age Z scores		Weight-for-length Z scores	
	Crude	**Adjusted [a]**	**Crude**	**Adjusted [a]**
	β (95% CI) P-value	**β (95% CI) P-value**	**β (95% CI) P-value**	**β (95% CI) P-value**
Total weight gain	0.02 (0.01, 0.04) 0.036	0.02 (0.01,0.04) **0 .044**	0.01(-0.01, 0.03) 0.151	0.01(-0.01,0.03) 0.187
Maternal age at parturition (per 1-y increase)		-0.01(-0.02, 0.01) 0.505		-0.01 (-0.02,0.01) 0.473
Prepregnancy BMI		0.04 (0.00, 0.06) **0.024**		0.04 (0.01, 0.07) **0.007**
Gestational age		0.07 (-0.02, 0.14) 0.113		0.06 (-0.02, 0.14) 0.111
Ethnicity				
Zhuang vs. others		-0.27 (-053, 0.03) 0.064[b]		-0.26 (-0.53, 0.04) 0.071 [b]
Mother's occupation				
Farmers vs. non- farmers		-0.28 (-0.49, -0.06) **0.010**		-0.28 (-0.48, -0.06) **0.012**
Offspring sex				
Female versus male		0.03 (-0.17, 0.21) 0.777		0.01(-0.19, 0.18) 0.966
Pregnancy Complication				
Yes vs. no		-0.30 (-0.68, 0.07) 0.091		0.68 (-0.72, 0.02) 0.087 [b]

[a] Adjusted for maternal age, maternal prepregnancy BMI, gestational age, ethnicity, occupation, pregnancy complication, and offspring's sex

[b] Borderline significance $p < 0.1$

Table 4.3. Crude and adjusted analysis between adequacy of GWG using IOM guidelines and weight-for-age Z-scores and weight-for-length Z scores

	Weight-for-age Z scores		**Weight-for-Length Z scores**	
	Crude	**Adjusted [a]**	**Crude**	**Adjusted [a]**
	β (95% CI) P-value	**β (95% CI) P-value**	**β (95% CI) P-value**	**β (95% CI) P-value**
GWG categories [b]				
Inadequate vs. adequate	-0.18 (-0.40, 0.03) 0.095	-0.17 (-0.38, 0.05) 0.118	-0.19 (-0.39, 0.03) 0.089 [c]	-0.18 (-0.38, 0.05) 0.138
Excessive vs. adequate	0.14 (-0.11, 0.42) 0.257	0.14 (-0.13, 0.40) 0.327	0.13 (-0.14, 0.39) 0.351	0.11 (-0.16, 0.38) 0. 423
Gestational age		0.07 (-0.01, 0.15) 0.078 [c]		0.07 (-0.01, 0.15) 0.070 [c]
Maternal age at parturition (per 1-y increase)		-0.001 (-0.02, 0.15) 0.932		-0.002 (-0.02, 0.01) 0.827
Ethnicity				
Zhuang vs. other ethnicities		-0.28 (-0.56, -0.01) **0.044**		-0.31 (-0.56, 0.00) **0.043**
Mother's occupation				
Farmers vs. non-farmers		-0.30 (-0.51, -0.08) **0.006**		-0.29 (-0.50, -0.08) **0.007**
Offspring sex				
Female vs. male		0.02 (-0.17, 0.21) 0.832		0.01 (-0.19, 0.17) 0.905
Pregnancy Complication				
Yes vs. No		-0.29 (-0.66, 0.09) 0.131		-0.33(-0.70, 0.04) 0.082 [c]

[a] Adjusted for maternal age, maternal prepregnancy BMI, gestational age, ethnicity, occupation, pregnancy complication, and offspring's sex

[b] Prepregnancy BMI used to calculate GWG categories: underweight (<18.5 kg/m^2), normal weight (≥18.5-23.9 kg/m^2), overweight (24.0-27.9 kg/m^2, and obese (≥28.0 kg/m^2).

[c] Borderline significance $p<0.1$

GWG: Gestational weight gain

Table 4.4. Direct and indirect effects of the association between GWG and weight-for-age z-scores at 1 year mediated through birthweight-for-gestational age

Gestational weight gain measures	Natural direct effect β (95% CI)	Natural direct effect P-value	Natural Indirect effect β (95% CI)	Natural Indirect effect P-value	Total Effect β (95% CI)	Total Effect P-value	Proportion mediated through birthweight
Weight-for-Age Z scores							
Total weight gain [a]	0.03(-0.02,0.05)	0.413	0.07(0.03,0.12)	<0.001	0.1 (0.00,0.23)	0.040	32.90
Adequacy of GWG [b]							
Inadequate vs. adequate	-0.08(0.31,0.11**)**	0.300	-0.11(-0.18, -0.03)	0.004	-0.19(-0.42,0.01)	0.060 [c]	47.61
Excessive vs. adequate	0.05(-0.06, 0.16)	0.347	0.06 (0.02,0.09)	0.003	0.11(-0.00,0.21)	0.075[c]	49.38
Weight-for-Length Z scores							
Total weight gain [a]	0.01(-0.08,0.11)	0.772	0.05 (0.02,0.08)	0.002	0.6(-0.03,0.15)	0.170	21.45
Adequacy of GWG [b]							
Inadequate vs. adequate	-0.09(-0.31,0.12)	0.380	-0.09 (-0.15, -0.02)	0.004	-0.18(-0.39,0.03)	0.060 [c]	47.50
Excessive vs. adequate	0.05(-0.06,0.16)	0.352	0.05 (0.01,0.08)	0.008	0.10(-0.02,0.20)	0.095 [c]	47.62

[a] Adjusted for maternal age, maternal prepregnancy BMI, gestational age, ethnicity, occupation, pregnancy complication, and offspring's sex
[b] Adjusted for maternal age, gestational age, ethnicity, occupation, pregnancy complication, and offspring's sex;
[c] Borderline significance p <0.1
GWG: Gestational weight gain

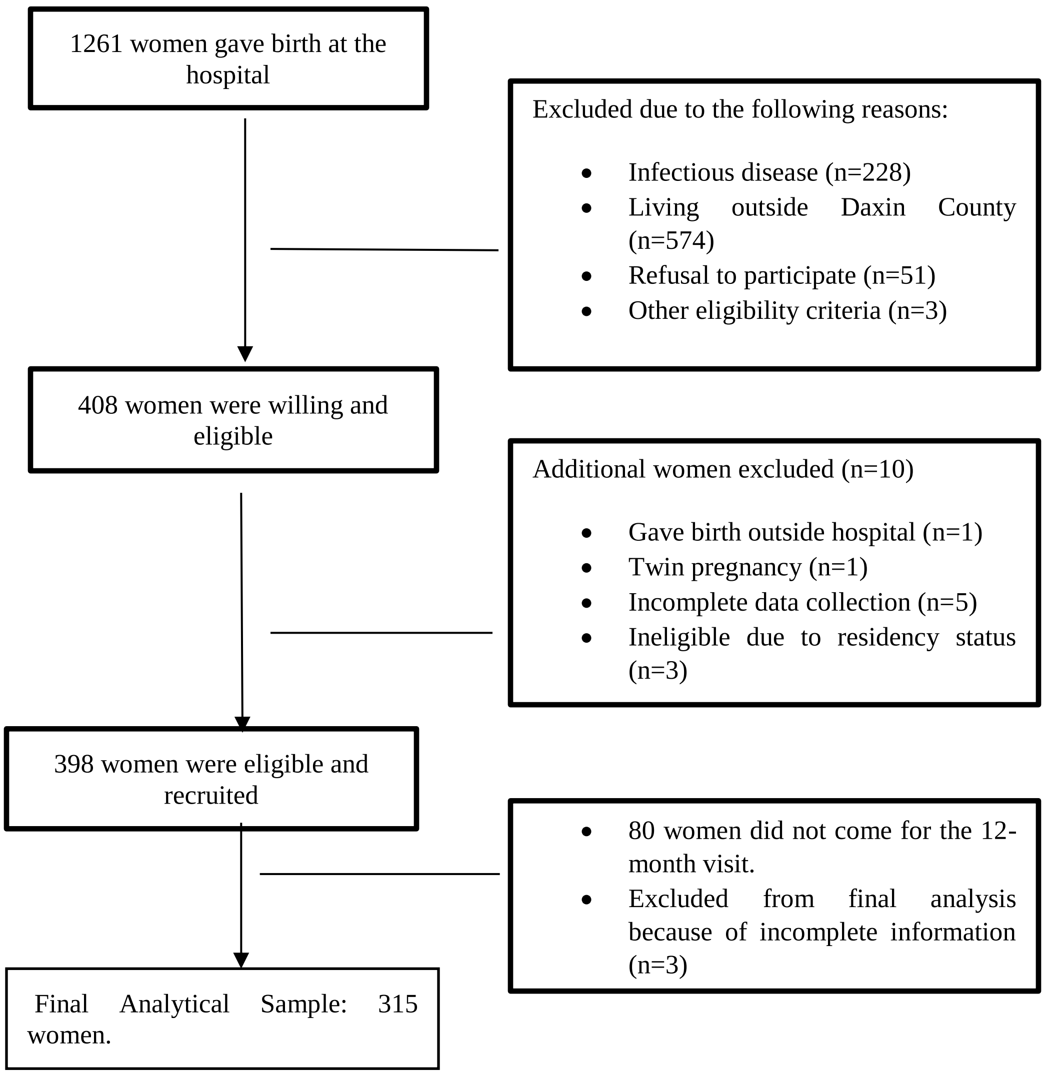

Figure 4.1. Flow Chart of Study Participants for Aim 1

CHAPTER 5

BREASTFEEDING PRACTICES AND ALLERGIC CONDITIONS AND ASTHMA AMONG A COHORT OF 6-YEAR-OLD US CHILDREN

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ABSTRACT

Background and Significance: Allergic conditions are common diseases in the United States. The objective of the study was to examine the association between meeting recommendations for breastfeeding and physician-diagnosed allergic conditions and asthma among 6-year-old US children.

Methods: Data came from the Infant Feeding Practices Study II (IFPS II) and its Year 6 Follow-up Study (Y6FU). A total of 1261 women with breastfeeding information were categorized according to exclusivity and duration of breastfeeding. Breastfeeding exclusivity was divided into four groups i.e. never breastfed, breastfed but not exclusively, exclusive breastfeeding < 4 months, and exclusive breastfeeding ≥ 4 months). Breastfeeding duration was categorized as > 0 to < 3 months, 3 to <6 months, 6 to <9 months, and ≥ 9 months. Multiple logistic regression analysis was used to examine allergic conditions and childhood asthma in association with breastfeeding patterns after adjusting for potential confounders.

Results: The prevalence of current physician-diagnosed hay fever/respiratory allergy, eczema/skin allergy, and asthma at 6 years old were 18.9%, 12.7%, and 6.5%, respectively. The proportion of mothers who never breastfed their infants was 13.8%, while 41.8% mothers breastfed but not exclusively, and additional 26.2% and 18.2% of mothers exclusively breastfed for < 4 months or ≥ 4 months, respectively. Compared with those who were exclusively breastfed for ≥4 months, children who were breastfed but not exclusively had 2.4 times higher adjusted odds of eczema/skin allergy (95% CI: 1.4, 4.3), while the odds of eczema/skin allergy among those who were exclusively breastfed for <4 months and the odds among those who never breastfed were not significantly different

from the reference group. We did not find significant associations between breastfeeding exclusivity and duration and hay fever /respiratory allergy or childhood asthma.

Conclusions: Our study examined the association between breastfeeding practices and allergic conditions and asthma but result were inconclusive. Therefore, the potential benefits of breastfeeding on allergies and childhood asthma cannot be ascertained from the study. Future studies could examine these associations using a data with objective assessments of allergic conditions.

INTRODUCTION

Allergic conditions, which include allergic rhinitis, hay fever, eczema, atopic dermatitis, and food allergy, have experienced a dramatic increase in the past decade particularly in westernized countries.[147-150] The estimated prevalence of sensitization to one or more common allergens is about 40-50% worldwide, and allergic rhinitis is estimated to affect 10-30% of the population globally.[147,149] In the United States, asthma is estimated to affect approximately 7 million children,[151] while hay fever and respiratory allergies affect 8.4% and 10% of children respectively.[150] Allergic conditions are the 6th leading cause of chronic illness in the U.S. with the annual cost estimated to be greater than $18 billion.[152] Thus, allergic conditions are common diseases in the United States and worldwide, and remain a significant cause of morbidity in early childhood with significant economic implications.[149]

A significant predictor of good health in infancy is proper feeding and nutrition. Breastfeeding is known to be the best source of infant nutrition in the first 6 months of life if there are no contraindications.[18] In 2012, the American Academy of Pediatrics (AAP) recommended exclusive breastfeeding for about 6 months, followed by continued breastfeeding for 12 months or longer as mutually desired by mother and infant with the introduction of complementary foods.[153] Apart from its content of carbohydrates, fat, and proteins, breast milk is also known to contain immunoglobulins and other immunocompetent cells, which may confer long-term protection against allergies.[23,154] Many studies have established the benefits of breastfeeding in promoting positive health outcomes in children.[20,21] However, its role in reducing or preventing the incidence of allergies or childhood asthma is inconclusive with some studies showing reduced risk of allergies,[23,24,96] and some showing increased risk[25,155,156] or no association.[157,158] Specifically, there remains a gap in knowledge on whether the exclusivity and duration of breastfeeding relate to allergies and asthma in children. Some studies have attributed these conflicting results to methodological differences in study designs (prospective versus retrospective, and interventional versus observational studies), study design flaws such as lack of information on duration of breastfeeding, exclusivity, case definition of each type of allergic condition, small sample size, and no consideration of observation time period (infancy, early childhood, adolescence).[89,96,157,159] Reverse causation is another proposed mechanism influencing the relationship between breastfeeding patterns and allergic condition in studies showing that breastfeeding increases the risk of developing allergies or asthma. It has been suggested that the increased risk of allergic condition seen with prolonged duration of breastfeeding may be due to the fact that the development of allergy symptoms cause mothers to prolong breastfeeding, thereby masking any protective effect of breastfeeding or leading to a false interpretation that the increased risk of allergy is a result of extended breastfeeding. [160]

Therefore, using a large dataset from a prospective cohort of US children recruited from pregnancy and followed up at 6 years of age, the present study examined the association between breastfeeding exclusivity and duration and the risk of having doctor-diagnosed allergic conditions (hay fever/ respiratory allergy, eczema/skin allergy) and asthma at age 6. We hypothesized that offspring of mothers who meet the AAP recommendation for breastfeeding exclusivity and duration would have a lower risk of allergic conditions and childhood asthma.

DATA AND METHODS

Study Sample

The Infant Feeding Practice Survey (IFPS) II was a consumer mail panel survey of US mothers and their newborn infants, which was conducted by the Centers for Disease Control and Prevention (CDC) in 2005-2007. The IFPS II is a longitudinal prospective cohort study of 4,900 women recruited in the third trimester of pregnancy with a focus on infant feeding practices throughout the first year of life, which were measured in neonatal period and at months 2, 3, 4, 5, 6, 7, 9, and 12 and on mothers' diet measured in their third trimester and at four months postpartum.[161] Of the 4900 women recruited at the third trimester, a total of 3,452 pregnant women were eligible for the postpartum follow-up. The criteria for the postnatal follow-up study are as follows: 1) mothers must be at least 18 years old at the time of prenatal questionnaire; 2) having singleton, full or nearly full-term (>35 weeks gestation) infants; 3) both mother and baby are healthy at birth; and 4) infant does not have an illness or condition likely to affect feeding at birth or during their first year of life. Information was collected from mothers using a series of mailed questionnaires administered nearly monthly from the mothers' seventh month of pregnancy through the first year of infancy.[120,121] The response rates for each postnatal questionnaire varied from 63% to 87%. [120]

In 2012, eligible mothers who were enrolled between 2005 -2007 were re-contacted to provide 6 years' follow-up information for their child and themselves. The primary objective of the follow-up study was to describe the health, behavior, developmental outcomes, and dietary patterns of offspring at age six.[161] Participants qualified for the Year 6 follow-up (Y6FU) study if they completed the neonatal questionnaire and were not disqualified after the neonatal questionnaire. Participants were excluded if there is 1) infant death 2) diagnosis of a condition likely to affect feeding, and 3) mothers living in a geographic area without postal service because of the Gulf Coast Hurricanes in 2005. The final eligible sample was 2958 mother-child pairs, but only 1,542 (≈52%) mother-child pair participated in the year 6 follow-up study[121] (Figure 1). The Y6FU provided additional data on the IFPS II cohort through a single questionnaire with information on allergic conditions, current health status, home environment, and food environment of offspring. After excluding missing values for variables essential to the multivariable analysis, the final analytic sample was 1261(Figure 1). Approval for IFPS II and its Y6FU was provided by the US Food and Drug Administration's Research Involving Human Subjects Committee and eligible mothers provided written informed consent.[120] Further descriptions of the IFPS II and Y6FU data are provided elsewhere. [120,121]

Study variables

The main outcome variable was mothers' self-report of physician diagnosis of allergic conditions (eczema or skin allergy, hay fever/respiratory condition and asthma) when the child was 6 years old. Mothers were asked if a doctor or other health professional ever told them that their 6-year-old had any of the itemized conditions: asthma, hay fever or respiratory allergy, eczema or any kind of skin allergy. If the mother answered yes, they were asked for current physician diagnosis of these conditions.

The main independent variable was breastfeeding practices, which was assessed from the IFPS II data. Breastfeeding patterns were assessed via 10 postpartum IFPS II questionnaire. Exclusive breastfeeding duration was calculated as offspring's age at the midpoint when the mother last reported feeding breast milk only and the first questionnaire when the mother first reported not exclusively breastfeed due to the introduction of other food or liquid apart from breast milk. If a mother exclusively breastfed through a given completed questionnaire, exclusive breastfeeding duration was set to infant's age when completing the last questionnaire. For mothers who reported they were still breastfeeding at the completion of their last questionnaire (n=464), we used breastfeeding duration in the Y6FU study (n=371) or last age at which the child received expressed breast milk (n=81). If both variables in the Y6FU were missing, we used the last age of breastfeeding duration in IFPS II (n=12).

Data on exclusive breastfeeding and overall breastfeeding duration were used to create our independent variables according to the AAP breastfeeding recommendations.[153] However, because of the low rates of 6-month exclusive breastfeeding duration (<5%), we used the cut-off point of ≥ 4 months which was suggested in the 2005 AAP recommendation that some infants may benefit from early complementary feeding from 4 months of age. We classified exclusive breastfeeding duration into 1) no breastfeeding, 2) non-exclusive breastfeeding, 3) exclusive breastfeeding < 4 months, and 4) exclusive breastfeeding ≥ 4 months. Breastfeeding duration was categorized into 1) no breastfeeding, 2) breastfeeding duration 1 to < 6 months, 3) breastfeeding duration 6 to < 12 months, and 4) breastfeeding duration ≥ 12 months.

Covariates were identified based on previous literature examining the impact of diet and breastfeeding patterns on the prevalence of allergic conditions and asthma.[122] Covariates from the IFPS II data included maternal education (high school or less; some college; college graduate; post graduate), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanics, and non-Hispanic others), poverty-income ratio (<185%, 185-350%, >350%), and type of delivery (vaginal or cesarean), child's sex (male or female), age of solid food introduction (< 4 months, 4 - <6 months, or ≥ 6 months), history of reported eczema before age 1 year (yes or no), and family history of allergy (yes or no). Mother's and other household member tobacco smoke exposure were obtained from the IFPS II and Y6FU data.

Statistical Analyses

Baseline maternal and offspring characteristics were described per exclusivity of breastfeeding using Chi-Square tests for categorical variables and analysis of variance (ANOVA) test for continuous variables. Multivariable logistic regression analysis was employed to evaluate the relationship between breastfeeding patterns and each of the following physician-diagnosis: 1) hay fever/ respiratory allergy 2) eczema/ skin allergy, and 3) childhood asthma at age 6. For each outcome, we adjusted for maternal race/ethnicity, education, household income, maternal smoking status, and other household member smoking status, family history of allergy (first-degree relatives), reported eczema at 1 year, parity, and child's sex. The inclusion of covariates in our models was based on findings from previous literature. [122,123] Because prior evidence in the literature has established family history of allergy and reported history of eczema as strong risk factors for the development of allergy,[123] we performed analyses with and without these risk factors. We also tested for interaction between breastfeeding and offspring sex and between breastfeeding and method of delivery based on literature identifying them as factors influencing atopy in childhood.[162-164] However, the interactions were not significant ($p<0.05$). We applied sequential modeling strategies by adjusting for different sets of covariates in two models, after our unadjusted analysis. In Model 2, we adjusted for maternal race, education, household income, method of delivery, maternal smoking status, parity, and child's sex. In Model 3, based on Model 2 we additionally adjusted for family history of allergy and reported eczema in infancy. In another model, we restricted the analysis to a subset of children classified as high-risk group if they had a family history of allergy or a reported history of eczema before age 1 and adjusted for covariates in Model 2. To limit the possibility of reverse causation, we performed additional analyses by excluding those who had eczema during infancy. Statistical significance was set at p–value < 0.05 and odds ratios (OR) and their 95% confidence intervals (CI) were reported. All analyses were performed using SAS version 9.4 (SAS Institute. Inc., Cary, NC).

RESULTS

Sample Characteristics

In this study population, mothers were mostly non-Hispanic white (89.2%) and had a college degree or graduate education (46%). About 14 % of mothers did not breastfeed their infants, while 41.6 % breastfed but not exclusively, 26.2% exclusively breastfed for <4 months, and 18.2% exclusively breastfed for ≥4 months. Among mothers who initiated breastfeeding, the mean duration of breastfeeding was 10.4 months, while mothers who breastfed exclusively for ≥ 4 months had a mean breastfeeding duration of 16.7 months. About 13% of mothers smoked during pregnancy. Nearly one-fifth of children (21%) had a positive history of eczema during the first year of life, while 62% had a positive family history of allergy (Table 5.1). Maternal education, race/ethnicity, method of delivery, poverty-income ratio, parity, maternal smoking and other household member smoking were significantly associated with exclusive breastfeeding duration ($p < 0.05$) (Table 5.1).

Prevalence of Allergic Conditions and Childhood Asthma

The prevalence of reported current physician diagnosis of hay fever/respiratory allergy, eczema/skin allergy, and asthma at 6 years old was 18.9%, 12.8%, and 6.5% respectively (Table 5.2). Exclusive breastfeeding duration ≥4 month was associated with lower prevalence (8.2%) of eczema/skin allergy compared to no breastfeeding (10.3%), non-exclusive breastfeeding (15.7%), and exclusive breastfeeding < 4 months (12.4%). There was no significant difference in prevalence rates of hay fever/respiratory allergy, and asthma according to exclusive breastfeeding duration and overall breastfeeding duration ($p>0.05$) (Table 5.2).

Breastfeeding and allergic conditions and childhood asthma

Table 5.3 shows the crude and adjusted odds of having allergic conditions and asthma according to breastfeeding practices. In the crude analysis, offspring who were not exclusively breastfed had higher odds of eczema/skin allergy when compared with offspring who had exclusive breastfeeding ≥4 months. (OR: 2.1, 95% CI: 1.07, 2.68). In model 2, this significant association remained after adjusting for covariates (OR: 2.4, 95% CI: 1.3-4.3). In addition, after additional adjustment for reported history of eczema and family history of allergy in model 3 we found a higher odds of eczema / skin allergy among non-exclusively breastfed children (OR: 1.8, 95% CI: 1.0-3.2). However, the odds of eczema/skin allergy among offspring who were exclusively breastfed for < 4 months (OR: 1.4, 95% CI: 0.6-2.0) and offspring who were never breastfed (OR: 1.2, 95% CI: 0.7-2.0) were not significantly different from the reference group -exclusive breastfeeding ≥ 4 months (Model 3). Also, we did not find significant associations between other categories of breastfeeding and childhood asthma, and hay fever /respiratory allergy, when compared with exclusive breastfeeding ≥4 months (Table 5.3).

We also analyzed the association between breastfeeding and allergic conditions and asthma by categorizing overall breastfeeding duration into four groups. Compared with breastfeeding duration ≥ 12 months, no breastfeeding, breastfeeding duration 1 to < 6 months, and breastfeeding duration 6 to < 12 months were not significantly associated with the odds of eczema/skin allergy. The odds of hay fever/respiratory allergy and asthma were not significantly different by breastfeeding duration (Table 5.4).

To assess possible reverse causation, we found that the mean duration of exclusive breastfeeding among children with infantile eczema (3.3 months) was not significantly different when compared to the duration of breastfeeding among children without infantile eczema (3.1 months; p=0.28). Second, in a subsample of infants without infantile eczema (n=998), results were similar to our primary analysis results. The odds of eczema/skin allergy were higher among non-exclusively breastfed infants compared to children who had exclusive breastfeeding ≥ 4months (OR: 2.0, 95% CI: 1.0-4.0). However, in the adjusted analysis, the odds ratio of eczema/skin allergy among offspring who were not exclusively breastfed remained higher but not statistically significant when compared to exclusive breastfeeding ≥ 4 months (OR. 1.7, 95% CI: 0.8-3.6). See Appendix B for Supplementary Table 1

High-Risk Group

We classified high-risk group as those with positive family history of atopy and reported eczema during the first year of life (n=750). Multivariate analysis examining the relationship between breastfeeding patterns and allergic diseases and asthma are shown in Model 4 of Table 5.3 and 5.4. However, no association was seen, suggesting no protective effect of breastfeeding on allergic conditions in this group.

Predictors of Allergic conditions

We assessed the association of sociodemographic and other background characteristics with allergic conditions and asthma. Table 5.5 shows variables related to allergic conditions from Model 3 of Table 3. Controlling for all other variables in Model 3, we found that the adjusted odds ratio for skin allergy at 6 years was about six times higher among those with reported eczema during the 1st year of life year compared to those without a prior history of eczema (OR: 6.3, 95% CI. 4.3 -9.3). Male sex and having two or more siblings was also associated with lower odds of skin allergy (P <0.05). The adjusted odd of hay fever /respiratory allergy was highest among those with a family history of allergy and those with reported history of eczema during the first year of life (OR: 2.3, 95% CI: 1.6-3.2; OR: 2.8 95% CI: 2.0-4.0 respectively). In addition, having 1 or more siblings was related to a lower odds of hay fever/ respiratory allergy in this cohort (p <0.05). Furthermore, reported history of eczema was associated with higher odds of asthma (OR: 2.0, 95% CI: 1.2-3.4).

DISCUSSION AND CONCLUSIONS

Our study examined the relationship between breastfeeding and allergic conditions and asthma among 6-year-old children using a national sample of the US population. The prevalence of asthma in our sample was 6.5% which is lower than the most recent (2014) national estimate of 10.6% among children 5-11 years.[165] However, the prevalence of current diagnosis of skin allergy (12.8%) and respiratory allergy (18.9%) were similar to the national prevalence rates of 13.1% and 17.4% respectively among 5-9 years. [150]

The present study found higher odds of skin allergy among non-exclusively breastfed children when compared to children who were breastfed exclusively for ≥ 4 months but did not find significant associations between exclusivity and duration of breastfeeding and respiratory allergy or asthma. The protective effect of longer duration of exclusive breastfeeding on eczema/skin allergy is consistent with previous studies.[29,166] On the other hand, the insignificant associations observed with hay fever/respiratory allergy and asthma are also consistent with previous studies.[157,158] A recent (2015) prospective cohort study conducted in Denmark with a sample size of about 400 children aged 7 years did not find significant associations between duration of exclusively breastfeeding and eczema, wheeze/asthma, or allergic rhinitis.[158] However, a cross-sectional study conducted in Japan among 1957 children aged 3 years found that exclusive breastfeeding greater than 4 months was associated with a lower prevalence of asthma but no association seen with wheeze or eczema. [167] This discrepant finding may be due to the difference in study design (cross-sectional[167] versus prospective cohort[158]) and age of participants (3 versus 7 years). It is difficult to establish temporal sequence with cross-sectional studies since the assessment of exposure and outcome is at a single time point and may be more prone to bias. Similar to our study design, the majority of studies examining the effect of breastfeeding on allergic conditions are mostly observational studies mainly due to ethical concerns with conducting randomized clinical trials. Recently Kramer et al. examined this association in a cluster randomized trial, but results were not supportive of a protective effect of prolonged and exclusive breastfeeding on asthma or allergic conditions by age 6.5 years which is similar to the age group of this present study.[157] Interestingly, the study found higher significant increases in positive skin prick test results with exclusive breastfeeding for 3 to <6 months and ≥6 months when compared to <3 months.[157] In contrast, the same author found a significant reduction in atopic eczema in a randomized trial among infants from the intervention sites, which were modeled based on the Baby Friendly Health Initiative (BHFI) and taught methods to maintain lactation, and promote prolonged and exclusive duration. [168]

In our sample, the adjusted OR of having skin allergy at 6 years was higher among those with reported history of eczema at 1 year, positive family history of eczema, and those who have 2 or more siblings. Surprisingly, male sex has a lower odds of skin allergy in our study sample which is not consistent with previous studies that identified male sex as a significant risk factor for the development of atopy. [123,163,169] However, a study conducted in Germany did find a higher prevalence of eczema in preschool girls than boys.[170] Mode of delivery and maternal education were not found to be significant predictors of allergic conditions and asthma in this cohort ($p > 0.05$).

With regards to exclusive breastfeeding duration, some researchers have suggested that prolonged duration of exclusive breastfeeding is associated with increased risk of eczema or atopic dermatitis and asthma.[155,156,171,172] One of the studies found that prolonged exclusive breastfeeding duration ≥ 2 months was associated with increased risk of eczema at the age of 2 and 5 years when compared with exclusive breastfeeding duration < 2 months.[156] However, more recent findings have suggested that reverse causation may be responsible for these findings [160] It has been inferred that history of atopic disease might influence mother's decision to prolong breastfeeding duration, thereby masking the protective effect of breastfeeding or leading to erroneous results that breastfeeding increases the risk of atopic diseases, when in fact, it was the development of allergic conditions that predisposes to prolonged breastfeeding duration.[160] Studies that have reported the increased risk of atopic dermatitis with prolonged breastfeeding duration have been criticized for failing to account for infantile eczema or family history of atopy which may have contributed to reverse causation. Our study ran different models with or without these risk factors and did a separate analysis excluding children with infantile eczema but did not find significant differences in our results. Moreover, the protective effect of exclusive breastfeeding ≥ 4 months was no longer seen. In addition, our findings did not show a significant difference in duration of exclusive breastfeeding between infants with infantile eczema and infants without these symptoms which suggest that reverse causation may not have influenced our findings.

The protective mechanisms of breastfeeding against allergies are not well-understood. Breast milk which contains many macronutrients (protein, fat, lactose and energy), micronutrients (vitamins and iodine), immunological factors (immunoglobulins (Ig) A, G, and M, lymphocytes, T cells), and growth factors are shown to provide many short- and long–term benefits including immunological and physical development. [77] The bioactive components such as secretory IgA, IgG, and transforming growth factor- β (TGF-β) in breast milk stimulate the immune system to fight infections and foreign agents.[77-79,173] However, it has also been proposed that breastmilk contents such as fatty acid may predispose to development of atopy.[174,175] Therefore, more studies are needed to investigate contents of breast milk and its association with atopy in offspring.

The present study examined protective breastfeeding patterns (breastfeeding duration > 12 months or exclusive breastfeeding duration > 4 months) against the development of allergic conditions. Recently, a systematic review and meta-analysis study found a protective effect of ever breastfeeding on asthma from 5-18 years when compared to never breastfeeding, but no significant association was found between exclusive breastfeeding greater than 3-4 months and asthma at 5-18 years.[176] The meta-analysis categorized studies into “more” or less” duration of breastfeeding based on the preferential selection of estimates for exclusivity, then duration (long vs. short). The study also found reduced risk of eczema below the age of 2 years when comparing exclusive breastfeeding greater than 3-4 months with other types of feeding but no association was found when comparing more versus less duration of breastfeeding. Moreover, a reduced risk of allergic rhinitis was found only below the age of 5 years when comparing more versus less duration of breastfeeding (OR:0.79, 95% CI: 0.63,0.98). [176] This meta-analysis may have been impacted by study heterogeneity secondary to the length of recall of breastfeeding. The authors explained that recall bias might occur from mothers with allergic children who made a conscious decision to breastfeed longer and therefore recall longer breastfeeding duration than mothers who do not have children with allergies.

The current study has some limitations. First, the sample is not nationally representative although it was nationally distributed and consists mainly of white, mostly educated women, which may limit its generalizability to the US population. Second, the assessment of allergic conditions was via mother’s self-reported physician diagnosis. We cannot ascertain if there was any diagnostic testing done and this may have predisposed to information bias. However, the possible measurement error in the assessment of allergic conditions is likely to be independent of breastfeeding status, and thus it would have biased our results towards the null. In addition, we only have current physician diagnosis of disease at 6 years, and thus we were unable to analyze according to age categories which might have helped us assess any variability of effect by age. Some studies have suggested that age may influence the relationship between breastfeeding and asthma.[25,155,177] The systematic review by Lodge et al. suggested that risk of allergy which is increased in older age group may be due to type of study and length of breastfeeding recall while the reduced risk of allergy seen in younger age group may be due to protective effect of breastfeeding on viral infections which may have been misdiagnosed as allergic diseases in this group.[158,176] Lastly, the completion rate of the questionnaire at 12 months postpartum and at the 6YFU study was relatively low (64.5% and 52%, respectively). Potential bias exists due to sample attrition in the IFPS 2 survey with findings showing that those who dropped out of the study were more likely to be younger, nonwhite, women of lower socioeconomic status and lower educational level, and live in the southern region of the country.[178] However, the potential selection bias resulting from sample attrition may not be an issue in a longitudinal prospective study because for bias to occur, selection of participants has to be related to both exposure and outcome. In this scenario, participants are not aware of the outcome of the study and have not experienced it. Although retention in the IFPS II survey may be related to the exposure, it was not related to our outcome of interest. Therefore the influence of selection bias in our study would be nonsignificant .

Despite the above-mentioned limitations, the present study has some unique strengths. The relatively large sample size (n=1261) in comparison to a few other published studies[123,158,167] on this relationship increased our statistical power to detect an association between variables of interest if any exists. The IFPS II data collected longitudinally and subsequent linkage to the Y6FU provide us the opportunity to examine associations between early nutrition and child's health at 6 years old. Because infant feeding practices were collected nearly monthly, the potential for recall bias was limited. The rich information on potential confounders enabled us to adjust for many covariates. In addition, survey questions on infant feeding practices and child's health including allergic conditions and asthma have already been validated and used in national surveys.[121] Lastly, the sub-classification into specific types of allergy enables us to have distinct outcome and analysis for each outcome.

Although, our study found higher odds of eczema/skin allergy among non-exclusively breastfed children in this cohort of US children when compared to exclusive breastfeeding ≥ 4 months, however, this association may be due to chance because of our inability to see an association between those who never breastfed when compared with the reference group i.e. no dose-response effect. In addition, findings from a cluster randomized trial examining the effectiveness of exclusivity and prolonged duration of breastfeeding on asthma and allergies among 6.5-year-old children,[157] did not support a protective effect of breastfeeding, which further suggests that our findings of a protective effect of breastfeeding may be due to chance. Furthermore, we did not see associations between duration of breastfeeding and allergic conditions and asthma at the age of` 6 years, and between exclusive breastfeeding duration and hay fever and asthma. Given the attributes of our sample population, overall, it appears that prolonged duration of breastfeeding is not protective against the development of allergic conditions and asthma is this cohort. Thus, potential benefits of breastfeeding on allergic conditions and childhood asthma cannot be ascertained from the study. Future studies using a nationally representative data and objective assessment of allergic diseases are still needed. Given other well-established benefits of breastfeeding, mothers should still be encouraged to follow the AAP recommendations for breastfeeding.

Table 5.1. Descriptive Characteristics of Participants of the Infant Feeding Practices Survey II according to exclusivity of breastfeeding

	Total	Never Breastfed	Breastfed but not exclusively	Exclusively breastfed for < 4 months	Exclusively breastfed for ≥4 months	P-value [a]
Total n (%)	1261	174 (13.8)	528 (41.8)	330 (26.2)	229 (18.2)	
Child's sex						0.347
Female	634 (50.4)	91 (52.3)	249 (47.3)	173 (52.4)	121 (52.8)	
Male	625 (49.6)	83 (47.7)	277 (52.7)	157 (47.6)	108 (47.2)	
Maternal education						**<0.0001**
High school or less	209 (16.6)	44 (25.3)	98 (18.6)	50 (15.2)	17 (7.4)	
Some College	470 (37.3)	73 (42.0)	190 (36.0)	141 (42.7)	66 (38.8)	
College graduate	440 (34.9)	47 (27.0)	179 (33.9)	108 (32.7)	106 (46.3)	
Post Graduate	142 (11.3)	10 (5.8)	61 (11.5)	31 (9.4)	40 (17.5)	
Race						**<0.001**
Non-Hispanic White	1097 (87.0)	159 (91.4)	431 (81.6)	296 (89.8)	211 (92.1)	
Non -Hispanic Black	45 (3.6)	8 (4.6)	25 (4.7)	11 (3.3)	2 (0.4)	
Hispanic	65 (5.2)	4 (2.3)	39 (7.4)	15 (4.6)	7 (3.1)	
Non –Hispanic Others	54 (4.2)	3 (1.8)	33(6.3)	8 (2.4)	10 (4.4)	
Poverty income Ratio						**0.018**
≤185%	449 (35.6)	83 (47.7)	176 (33.3)	110 (33.3)	80 (34.9)	
>186-300%	333 (26.4)	41 (23.6)	135 (25.6)	96 (29.1)	64 (26.6)	
≥300%	479 (38.0)	50 (28.7)	217 (41.1)	124 (37.6)	85 (38.4)	
Maternal tobacco smoke						**<0.0001**
Yes	164 (13.0)	39 (22.5)	71 (13.5)	50 (15.2)	4 (1.75)	
No	1096 (87.0)	134 (77.5)	457 (86.5	280 (84.8)	225 (98.3)	
Others household member tobacco smoke exposure						**<0.0001**
Yes	151 (12.0)	43 (24.9)	68 (13.0)	36 (11.0)	4 (1.8)	
No	1102 (88.0)	130 (75.1)	457 (87.0)	292(89.0)	223 (98.2)	
Family history of allergy						0.118

No	472 (37.4)	71 (40.8)	209 (39.6)	106 (32.1)	86 (37.4)	
Yes	789 (62.6)	103 (59.2)	319 (60.4)	224 (67.9)	143 (62.6)	
History of eczema before age 1						0.146
No	998 (79.1)	145 (83.3)	422 (79.9)	261 (79.1)	170 (74.2)	
Yes	263 (20.9)	29 (16.7)	106 (20.1)	69 (20.9)	59 (25.8)	
Type of delivery						**<0.0001**
Vaginal	888 (70.4)	104 (59.8)	346 (65.5)	258 (78.2)	176 (78.6)	
Caesarean	373 (29.6)	70 (40.2)	182 (34.5)	72 (21.8)	49 (21.4)	
Parity						**0.026**
0	123 (9.9)	18 (10.4)	58 (11.2)	34 (10.5)	13 (5.7)	
1	507 (40.9)	78 (45.4)	224 (43.3)	120 (36.9)	85 (37.44)	
2+	611 (49.2)	76 (44.2)	235 (45.5)	171 (52.6)	129 (56.83)	
Breastfeeding duration (month), median (IQR)	8.2 (8.9)	N.A.	4.5 (1.3-11.8)	6.5 (3.0-11.9)	13 (11.0-16.3)	**<0.0001**

[a] Based on Chi-square test for categorical variables and ANOVA test for continuous variable
IQR:Interquartile range

Table 5.2. Prevalence of Allergic Conditions and Asthma at 6 Years of Age According to Breastfeeding Practices

		Physician diagnosed conditions* among 6-year-olds (%)		
Variables	N	**Eczema/Skin Allergy (%)**	**Hay Fever / Respiratory Allergy (%)**	**Asthma (%)**
Total	1261	12.8	18.9	6.4
Ever Breastfed				
No	174	13.2	18.4	6.3
Yes	1087	10.3	19.4	6.4
		P=0.30 [a]	P=0.80	P=0.99
Breastfeeding Duration				
0 months	174	10.3	18.4	6.3
1 to < 6 months	427	13.1	18.5	5.6
6 to < 12 months	294	12.6	16.7	5.8
≥12 months	366	13.7	21.3	7.9
		P=0.75	P=0.49	P=0.57
Exclusive Breastfeeding Duration				
No breastfeeding	174	10.3	18.4	6.3
Breastfeeding but no exclusivity	528	15.7	20.6	7.0
Exclusive breastfeeding < 4 months	330	12.4	18.2	6.7
Exclusive breastfeeding ≥ 4 months	229	8.3	16.2	4.8
		P=0.03[a]	P=0.51	P=0.72

[a] Based on Chi-square test and statistical significance set at $p < 0.05$

*Mother's self-report

Table 5.3. Adjusted Odds Ratio for Allergic Disorders and asthma among 6-Year-Olds US children According to Exclusivity of Breastfeeding

Variables	Odds Ratio (OR) and 95% Confidence Interval			
	Model 1	**Model 2**	**Model 3**	**Model 4**
Eczema / Skin allergy				
No breastfeeding	1.3 (0.7-2.5)	1.3 (0.6-2.7)	1.5 (0.7-3.2)	1.5 (0.6-3.2)
Breastfeeding, but no exclusivity	**2.1 (1.2- 3.5)**	**1.8 (1.1-3.2)**	**2.4 (1.4-4.3)**	1.7 (0.9-3.1)
Exclusive breastfeeding $<$ 4 months	1.6 (0.9-2.8)	1.4 (0.7-2.5)	1.7 (0.9-3.2)	1.3 (0.7-2.7)
Exclusive breastfeeding $\geq$ 4 months	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference
Hay Fever/ Respiratory Allergy				
No breastfeeding	1.2 (0.7-2.0)	1.2 (0.7-2.1)	1.3 (0.7-2.3)	1.2 (0.6-2.4)
Breastfeeding, but no exclusivity	1.4 (0.9-2.0)	1.2 (0.7-2.0)	1.5 (0.9-2.8)	1.3 (0.8-2.1)
Exclusive breastfeeding $<$ 4 months	1.2 (0.7-1.8)	1.0 (0.6-1.6)	1.2 (0.7-1.9)	1.0 (0.6-1.7)
Exclusive breastfeeding $\geq$ 4 months	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference
Asthma				
No breastfeeding	1.4 (0.6, 3.2)	1.4 (0.6-3.7)	1.5 (0.6-3.6)	1.4 (0.5-4.3)
Breastfeeding, but no exclusivity	1.5 (0.8-3.0)	1.5 (0.7-3.1)	1.4 (0.7-2.9)	1.6 (0.7-3.8)
Exclusive breastfeeding $<$ 4 months	1.4 (0.7-3.0)	1.3 (0.6-3.0)	1.4 (0.6-3.0)	1.5 (0.6-3.9)
Exclusive breastfeeding $\geq$ 4 months	1.0 Reference	1.0 Reference	1.0 Reference	1. 0 Reference

Model 1: Unadjusted
Model 2: Adjusted for maternal race, education, income, method of delivery, maternal smoking status, parity, age of solid food introduction, and child's sex
Model 3: Adjusted for covariates in Model 2 and family history of allergy, and reported eczema in infancy
Model 4: Restricted to infants with family history of allergy, and reported eczema in infancy (n=750) and adjusted for covariates in Model 2

Table 5.4: Adjusted Odds for Allergic Disorders and Asthma among 6-Year-Old US children according to breastfeeding duration

	Odds Ratio (OR) and 95% Confidence Interval			
Variables	**Model 1**	**Model 2**	**Model 3**	**Model 4**
Eczema / Skin allergy				
Breastfeeding Duration - 0 months	0.8 (0.4-1.3)	0.9 (0.5-1.8)	0.8 (0.4-1.6)	0.9 (0.5-1.9)
Breastfeeding Duration - >0 to < 6 months	1.0 (0.6-1.4)	1.1 (0.7-1.7)	1.0 (0.7-1.7)	0.9 (0.5-1.5)
Breastfeeding Duration - 6 to < 12 months	0.9 (0.6-1.4)	1.1 (0.7-1.8)	1.1 (0.7-1.8)	0.9 (0.5-1.6)
Breastfeeding Duration - ≥12 month	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference
Hay Fever/ Respiratory Allergy				
Breastfeeding Duration - 0 months	0.8 (0.5-1.3)	0.9 (0.5-1.40	0.9 (0.5 -1.5)	0.9 (0.5-1.5)
Breastfeeding Duration - >0 to < 6 months	0.8 (0.6-1.2)	0.8 (0.6-1.2)	0.8 (0.6 -1.3)	0.8 (0.5-1.2)
Breastfeeding Duration - 6 to < 12 months	0.7 (0.5-1.1)	0.7 (0.5-1.1)	0. 8 (0.5-1.2)	0.5 (0.4-1.0)
Breastfeeding Duration - ≥12 months	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference
Asthma				
Breastfeeding Duration - 0 months	0.8 (0.4-1.6)	0.7 (0.4-1.6)	0.8(0.4-1.7)	0.7 (0.3-1.8)
Breastfeeding Duration - >0 to < 6 months	0.7 (0.4-1.2)	0.6 (0.3-1.1)	0.6(0.3-1.1)	0.6 (0.3-1.3)
Breastfeeding Duration - 6 to < 12 months	0.7 (0.4-1.3)	0.7 (0.4-1.3)	0.6(0.4-1.1)	0.7 (0.4-1.5)
Breastfeeding Duration - ≥12 months	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference

Model 1: Unadjusted
Model 2: Adjusted for maternal race, education, income, method of delivery, maternal smoking status, parity, age of solid food introduction, and child's sex
Model 3: Adjusted for covariates in Model 2 and family history of allergy, and reported eczema in infancy
Model 4: Restricted to infants with family history of allergy, and reported eczema in infancy (high-risk group) and adjusted for covariates in Model 2

Table 5.5. Adjusted odds ratio (AOR) of allergic conditions and asthma with background characteristics

	Eczema/ Skin Allergy AOR (95% CI)	Hay Fever / Respiratory allergy AOR (95% CI)	Asthma AOR (95% CI)
Total n, %	170 (12.8)	252 (18.9)	89 (6.7)
Child's sex			
Female	1.0 ref	1.0 ref	1.0 ref
Male	0.7 (0.4-0.9)	0.9 (0.7-1.3)	1.1 (0.8-1.9)
Maternal education			
High school or less	1 .0 ref	1 ref	1 ref
Some College	1.2 (0.7-0.2)	1.1 (0.7-1.6)	1.5 (0.7-3.3)
College graduate	1.0 (0.6-1.9)	1.4 (0.8-2.4)	1.7 (0.8-4.1)
Post Graduate	1.2 (0.6-2.5)	1.3 (0.7-2.40	0.9 (0.3-2.7)
Race			
Non-Hispanic White	1 ref	1 ref	1 ref
Non -Hispanic Black	0.8 (0.3-1.9)	0.6 (0.2-1.4)	1.2 (0.4-3.7)
Hispanic	1.6 (0.8-3.5)	1.0 (0.5-2.0)	1.7 (0.7-4.3)
Non –Hispanic Other	1.6 (0.7-3.8)	0.8 (0.4-1.9)	2.3 (0.9-5.9)
Poverty income ratio			
≤185%	1 ref	1 ref	1 ref
186-300%	0.8 (0.5-1.3)	1.2 (0.8-1.8)	0.7 (0.3-1.3)
≥300%	0.9 (0.5-1.4)	1.1 (0.7-1.6)	0.9 (0.5-1.6)
Mothers smoking status			
Smoker	1 ref	1 ref	1 ref
Nonsmoker	0.8 (0.4-1.4)	0.9 (0.5-1.6)	1.1 (0.5-2.3)
Family history of allergy			
No	1 ref	1 ref	1 ref
Yes	1.2 (0.8-1.8)	**2.3 (1.6-3.2)**	1.3 (0.8-2.2)
Infantile eczema			
No	1 ref	1 ref	1 ref
Yes	**6.3 (4.3-9.3)**	**2.8 (2.0-4.0)**	**2.0 (1.2-3.4)**
Type of delivery			
Vaginal	1 ref	1 ref	1 ref
Caesarian	1.2 (0.8-1.8)	1.0 (0.7-1.4)	1.0 (0.6-1.7)
Parity			
0 Sibling	1	1	1
1 Sibling	0.7 (0.4-1.2)	**0.5 (0.3-0.8)**	0.6 (0.3-1.3)
2+ Sibling	0.5 (**0.3-0.9**)	**0.4 (0.3-0.7)**	0.6 (0.3-1.3)

[a] Statistical significance set at $p < 0.05$

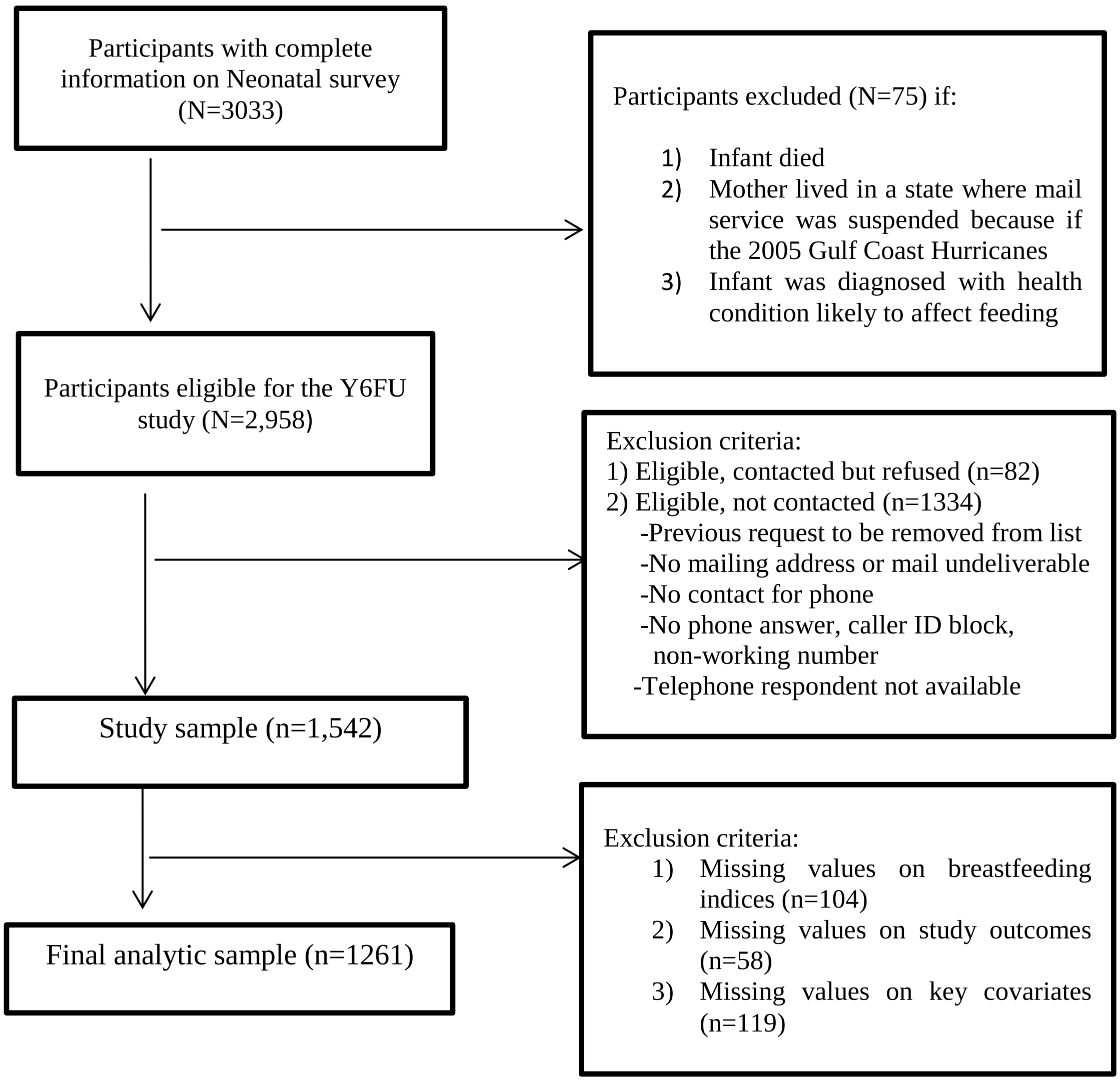

Figure 5.1. Flow Chart of Study Participants for Aim 2

CHAPTER 6

BREASTFEEDING PRACTICES AND POSTPARTUM WEIGHT RETENTION AT 1 YEAR AMONG A COHORT OF US MOTHERS

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Abstract

Introduction: The association between breastfeeding and postpartum weight retention is still not clear. Our objective was to investigate the association between breastfeeding practices (intensity and duration) and postpartum weight retention.

Methods: Data came from the Infant Feeding Practices Study (IFPS) II. A total of 1287 women with self-reported breastfeeding information, prepregnancy and postpartum weight were included. Multivariable linear regression models were used to examine postpartum weight at 12 months, and generalized estimating equations for repeated measurements were used to examine postpartum weight at 6, 9, and 12 months in association with breastfeeding intensity after adjusting for known confounders.

Results: On average, women retained 2.8 lbs. (SD: 15.6) at 12 months postpartum. About 24% of participants were obese prior to pregnancy. Compared with high breastfeeding intensity (>80% of milk feedings were breastmilk), low (<20%) and medium breastfeeding intensity (20-80%) were associated with higher postpartum weight retention (β=3.6, p=0.003; β=2.8 p=0.047, respectively). When stratified by prepregnancy BMI, this association remained significant among normal weight women, but not among overweight and obese women. In addition, breastfeeding duration assessed as a continuous measure was also associated with postpartum weight retention among all women. Among normal weight women, there was a significant reduction in postpartum weight i.e. for every 1-week increase in breastfeeding; women lost 0.09 lbs. in weight. In the longitudinal analysis, low and medium breastfeeding intensity were associated with higher postpartum weight retention over time (β=3.3; 95% CI: 1.4, 5.4; β=2.0; 95% CI: 0.5, 4.0, respectively) when compared with high breastfeeding intensity.

Conclusions: Our study found that high breastfeeding intensity and duration was associated with lower postpartum weight retention at 12 months and over time during the 12-month period. Encouraging women to breastfeed in combination with healthy lifestyle behavior may help reduce postpartum weight retention.

INTRODUCTION

Obesity has become a significant public health problem in the United States. Recent estimates show that 37% women of reproductive age (20-39 years) are obese.[37] While lifestyle and sociodemographic factors are shown to play a significant role in weight gain among women, some studies have shown that postpartum weight retention among women can lead to increased risk for overweight and obesity in women, which is ultimately associated with cardiometabolic disorders[33-35] and increased risk of cancers.[36]

In 2012, the American Academy of Pediatrics (AAP) emphasized its previous recommendation of exclusive breastfeeding for about 6 months, followed by continued breastfeeding till 12 months or longer as mutually desired by mother and infant and introducing complementary foods at 6 months.[19] Many studies have established the positive benefits of breast milk among children including increased resistance to infections, reduction in episodes of respiratory diseases, gastrointestinal disease, otitis media, Sudden Infant Death Syndrome (SIDS), and reduced risk of Type 1 and Type 2 diabetes mellitus in childhood.[21,73,74,80,82] In addition, breastfeeding has a positive effect in reducing the risk of hypertension[179] and breast or ovarian cancers for mothers later in life.[29,30,180] However, its role in reducing postpartum weight is less well established, and results are mixed.[2,32,181]

It has been proposed that lactation promotes regional fat mobilization and increases total energy expenditure, which subsequently reduces postpartum weight.[110,182,183] However, results from studies examining this relationship have been conflicting with some showing that breastfeeding is associated with reduction in postpartum weight[106,184] while others showed no association.[2,29,181] A recent randomized controlled clinical trial found that breastfeeding initiation and breastfeeding duration less than 6 months was not associated with weight retention in mothers at 6 months postpartum.[181] An observational study found no significant association between adherence to AAP breastfeeding recommendations and maternal weight at 6 years post-delivery among normal and overweight women, while obese women with complete adherence to breastfeeding recommendations had less weight retention than women who never breastfed (-8.0 kg).[185] While some studies showed that prolonged duration of breastfeeding reduces postpartum weight retention,[2,32] few studies have examined how breastfeeding intensity, defined as the proportion of milk feedings that is breast milk, influences postpartum weight retention. Given low rates of exclusive breastfeeding duration at 40.4% and 22.2% at 3 and 6 months, respectively,[186] it would be more important to assess the quantity of breast milk in relation to other milk feedings and its impact on postpartum weight loss. In addition, breast milk intensity and duration have also been suggested as a means of energy expenditure for the mothers, which may have a direct impact on weight loss during the postpartum period.

Therefore, using the data from a prospective cohort study of US mothers with a relatively large sample size and multiple assessments of breastfeeding practices, we examined the association between breastfeeding practices (defined as intensity and duration) and postpartum weight retention at 12 months and through the first year after delivery among US mothers.

DATA AND METHODS:

Study sample

Data came from the 2005-2007 Infant Feeding Practice Survey (IFPS) II, which was a prospective cohort study conducted by the Centers for Disease Control and Prevention and the US Food and Drug Administration. Participants were recruited during the third trimester of pregnancy using a consumer-opinion mail panel survey. The study consisted initially of 4,902 women, but approximately 2,000 women and their infants were followed through one year of life. Following delivery, women who met the following eligibility criteria were followed in the postpartum study: 1) mothers must be at least 18 years old at the time of prenatal questionnaire; 2) singleton and full or nearly full-term infants; 3) both mother and baby are healthy at birth; and 4) the infant does not have an illness or condition likely to affect feeding at birth or during their first year of life. Data were collected via mothers' self-report using a last-trimester questionnaire and series of 10 mailed questionnaires administered nearly monthly through the first year of infancy.[120,121] Apart from feeding practices, IFPS II also collected information on maternal sociodemographic characteristics, maternal diet, and health. Detailed descriptions of the study are provided elsewhere.[120] The Food and Drug Administration's Research Involving Human Subjects Committee provided approval for the study.

Study variables

Outcomes: Postpartum weight retention at 12 months

Prepregnancy weight in pounds was assessed using the prenatal questionnaire. On the 6, 9, and 12 months' postpartum questionnaire, mothers were asked to estimate how much they weighed in pounds. Postpartum weight retentions at 6, 9, and 12 months were calculated as the difference between weight at those time points and mother's prepregnancy weight.

Exposure: Breastfeeding Practices

Breastfeeding practices were assessed by breastfeeding intensity and breastfeeding duration during the first year. Breastfeeding intensity was defined as the proportion of milk feedings that were breast milk. Breastfeeding information was obtained via 10 postpartum self-reported survey questionnaires. Mothers were asked 1) did you ever breastfeed your child? 2) How old was your baby when you completely stopped breastfeeding and pumping milk? 3) In the past seven days, how often was your baby fed each food listed - breastmilk, formula, cow's milk, other milk, other dairy, soy etc.? Mothers were also asked to give an estimate of the average number of times they feed their infants with formula, and other types of milk including breast milk, cow milk, and other milk such as soy, rice, and goat milk. Breastfeeding intensity was calculated as the proportion of the number of breastfeeding milk feeding over the total number of milk feedings including breast milk, formula, cow's milk, and other milk feedings.[124] We derived the mean breastfeeding intensity during the first 6 months of infancy if mothers completed 3 or more responses on breastfeeding intensity in the first 6 postpartum questionnaires. We categorized breastfeeding intensity into 1) high (if > 80% of milk feedings were breast milk), 2) medium (20-80%), and 3) low (<20%). Women who never breastfed were included in low intensity group. We also assessed breastfeeding duration from IFPS II. Mothers were asked if they had completely stopped breastfeeding and pumping milk for their infants and if they answered "yes," they were also asked how old their baby was when they stopped breastfeeding and pumping milk. Breastfeeding duration during 12 months of follow-up was categorized into 1) breastfeeding duration > 0 to < 3 months 2) breastfeeding duration 3 to < 6months 3) breastfeeding duration 6 to < 9months and 4) breastfeeding duration ≥ 9 months.

Covariates

Based on the literature,[2] known confounding variables were identified. They are: maternal education (high school or less, some college, college graduate, and post-graduate), maternal race (Whites and non-Whites), poverty–income ratio (≤185%, 186%-300%, and >300%), marital status (married, unmarried), parity (nulliparous, multiparous), prepregnancy body mass index (BMI< 25 kg/m^2, 25 to < 30kg/m^2 , ≥ 30 kg/m^2), postpartum maternal smoking (yes and no), and meeting the 2009 Institute of Medicine guidelines for gestational weight gain (inadequate, adequate, or excessive). Because of the low number of underweight women in our cohort (n=46), we categorized normal weight as BMI (<25 kg/m^2). Using BMI classification and IOM guidelines, weight gain was categorized as inadequate, adequate, and excessive weight gain if weight gain is below, appropriate, or above the recommendations, respectively.[46]

Statistical analysis

Baseline maternal characteristics were described and compared according to breastfeeding intensity using Chi-Square tests for categorical variables and ANOVA test for continuous variables. Multivariate linear regression models were used to examine the association between breastfeeding intensity and weight retention at 12 months postpartum while adjusting for covariates Our analysis for the multivariate linear regression was based on complete-case analysis and mothers with missing data were excluded. After excluding women with no information at 12 months and missing information on our main variables and key covariates, a total of 1287 women were included in our final analytical sample. (See flow diagram). We compared the characteristics of our study sample with participants who are excluded using chi-square and ANOVA tests for categorical and continuous variable, respectively. We also evaluated the association between duration of breastfeeding and postpartum weight retention at 12 months. Because studies have shown that breastfeeding has a significant association with prepregnancy BMI, that is, overweight and obese women are less likely to breastfeed for a long time,[106,187,188] we tested interaction between prepregnancy BMI and breastfeeding duration, thus, our results were presented by accounting for effect modification by prepregnancy BMI. Significant interaction was set at $p < 0.2$. Based on the literature and statistical significance ($p < 0.1$) of the bivariate analysis, the following variables were adjusted for in the multivariable analysis: maternal age, race, parity, income, maternal education, marital status, postpartum smoking, and gestational weight gain.

To examine the average effect of breastfeeding practices on postpartum weight change over time, we used generalized linear models (GENMOD) procedure to analyze the longitudinal data with repeated assessment of postpartum weight changes at 6, 9, 12 months. For the longitudinal analysis, using generalized estimating equations, we analyzed using 1) data with complete case analysis (n=1287) and 2) the full sample without excluding any missing data (n=1692). The GENMOD procedure analyzes correlated data with higher statistical efficiency. This longitudinal design allowed us to examine patterns of change over 1 year postpartum. In addition to the covariates adjusted for earlier, we further adjusted for the months at each postpartum measurement visit. The correlation structure used was the exchangeable term which assumes that the correlation between any two responses of one individual is the same. The choice of our correlation structure was based on the Quasi-information criterion (QIC),[189] and the biological rationale[189,190] that the correlation of postpartum weight measurement in the same individual is the same. Statistical significance was set at $p < 0.05$ and all analyses were performed using SAS software (version 9.4; SAS Institute, Inc. NC)

RESULTS

Of the total 1692 eligible mothers, 405 women were excluded because of missing data. Compared with our final study sample, a higher proportion of excluded mothers were non-white (19.6% vs. 10.6%, $p < 0.0001$), smoked during postpartum (42.0% vs. 18.2%, $p < 0.0001$), had a high school education or less (35.9% vs. 17.9%, $p < 0.0001$), while a smaller proportion of excluded mothers were nulliparous (64.9 % vs 73.1%, $p = 0.002$), and were unmarried (63.6% vs. 84.0%, $p < 0.001$). Excluded mothers also had significantly higher postpartum weight retention at 12 months compared with our study sample (6.6 lbs. vs. 3.1 lbs., $p < 0.001$). However, there was no significant difference between excluded mothers and included mothers according to categories of breastfeeding duration. (data not shown)

Table 6.1 shows the descriptive characteristics of mothers according to breastfeeding intensity during the first 6 months postpartum. Of the 1287 women in our final analytical sample, in the first 6 months of life 49.2% (n=622) of mothers had a high breastfeeding intensity rate, while 34.7% (n=447) and 16.7% (n=215) had low and medium breastfeeding intensity rates, respectively. The mean age of mothers was 30.3 years (SD=5.1). Approximately 89% of mothers were White, while about 50% had a college or postgraduate education. Most mothers were married (84.5 %) and only 26.8% were nulliparous. On average, 24% of women in our study were obese, and 25% were overweight. The mean gestational weight gain was 30.9 lbs., with 46.7% of women gaining above the Institute of Medicine recommended weight during pregnancy. In addition, race, poverty income ratio, education, maternal smoking, marital status, parity, and prepregnancy BMI were significantly related to breastfeeding intensity at $p < 0.05$ (Table 6.1).

Table 6.2 shows the mean weight retention according to breastfeeding intensity during the first 6 months, stratified by prepregnancy BMI. The interaction term between breastfeeding duration and BMI was significant at $p = 0.192$. On average, women retained 2.8 ± 15.6 lbs. at 12 months postpartum (data not shown). Among all women, mean weight retention at 12 months differed by the average breastfeeding intensity ($p=0.047$). Women who had high breastfeeding intensity had significantly lower mean weight retention (1.7 lbs.) compared with women with low breastfeeding intensity (4.2 lbs.). Among normal weight women, the mean weight retention also decreased with higher breastfeeding intensity ($p < 0.001$). However, there was no significant difference in mean weight retention according to breastfeeding intensity among overweight and obese women at 12 months postpartum.

Table 6.3 shows the adjusted analysis between breastfeeding measures and postpartum weight retention in all women and in sub-samples by maternal prepregnancy BMI. Among all women, all measures of breastfeeding were associated with postpartum weight retention ($p < 0.05$). When compared with high breastfeeding intensity, low intensity and medium breastfeeding intensity was associated with higher postpartum weight retention (β=3.6 lbs., p=0.003; β=2.6 lbs., p=0.047, respectively). However, when stratified by prepregnancy BMI, this association only remained among normal weight women. (β=4.5 lbs., p=0.003; β=2.8 lbs., p=0.049, respectively) with no significant associations seen among overweight and obese women.

Similarly, breastfeeding duration (continuous variable) was significantly associated with postpartum weight retention among all women, that is, women lose an average of 0.08 lbs. with every 1-week increase in breastfeeding duration. This association remained among normal weight women only (β=-0.09 lbs; 95% CI: -0.14, -0.05; p=0.003) i.e. for every 1-week increase in breastfeeding; women lost 0.09 lb. in weight. Similar results were seen with categorical measures of breastfeeding duration among normal weight women. When compared with breastfeeding duration >9 months, breastfeeding duration <3 months was associated with higher postpartum weight retention at 12 months after delivery (β=6.5; 95% CI: 3.6, 9.4) (Table 6. 3).

Table 6.4 shows results of the longitudinal analysis using the generalized estimating equations. Compared to high breastfeeding intensity, low and medium breastfeeding intensity were associated with higher postpartum weight retention over time (β =3.4 lbs.; 95% CI: 1.6, 4.9; β =2.1 lbs.; 95% CI: 0.7, 4.0, respectively). Postpartum time in weeks was a significant negative predictor of postpartum weight retention (β = -0.2 lbs..; 95% CI: -0.3, -0.1). Over time, mothers with low maternal education (high school or less) retained higher postpartum weight when compared with mothers with postgraduate education (β =3.7 lbs.; 95% CI: 0.7, 6.7). On average, it appears obese and overweight women retained less postpartum weight compared to their normal weight counterpart over time (-9.6 lbs. and -3.5 lbs. respectively). When we analysed using the full sample (n=1692), the GEE results were similar except the significant association seen with unmarried retaining more weight over time compared to married women (β =2.7 lbs.; 95% CI: 0.3, 5.1; p <0.03). (See Appendix C for supplementary table 1)

Sensitivity Analysis in a subsample of mothers with information on caloric intake

The IFPS II main survey does not include information on maternal caloric intake, therefore we were unable to adjust for this variable in our main analysis. However, maternal dietary assessments were conducted in a subsample of IFPS II respondents at 3-4 months postpartum using the 149 item Diet History Questionnaire (DHQ), which is a modified version of the National Cancer Institute (NCI) dietary questionnaire. A total of 1469 women completed the dietary questionnaire; however, after excluding women with extreme values per NCI guidance, the final DHQ sample was 1422. Women with missing information on postpartum weight at 12 months and breastfeeding intensity were excluded, which resulted in 871 women for our sensitivity analysis in a sample of women with information on postpartum caloric intake. we conducted multivariate linear regression to assess the relationship between breastfeeding and postpartum weight at 12 months (n=871), while accounting for confounding factors such as maternal caloric intake and other previously-mentioned covariates. In addition, we assessed the average postpartum weight retention over time (6, 9, 12 months) in relation to breastfeeding intensity using the full sample (n=1389).

Supplementary Table 2 in Appendix C shows the adjusted analysis between breastfeeding measures and postpartum weight retention in all women and in sub-samples by maternal prepregnancy BMI. Among all women, only categories of breastfeeding intensity were associated with postpartum weight retention. When compared with high breastfeeding intensity, low intensity and medium breastfeeding intensity were both associated with higher postpartum weight retention (β=2.7 lbs., p=0.043; β=3.1 p=0.043, respectively). Continuous breastfeeding duration was associated with postpartum weight retention at borderline significance i.e. for every 1 week increase in breastfeeding duration, mothers lost 0.05lbs. of weight. (p=0.06). The significant associations seen with categorical measures of breastfeeding duration in our main analysis were no longer present.

Among normal weight women, medium breastfeeding intensity was associated with higher postpartum weight retention when compared with high breastfeeding intensity (β=4.3lbs., p=0.014), but this association was not significant in any category of breastfeeding intensity among overweight and obese women. In addition, we did not find any association between continuous measure of breastfeeding and postpartum weight retention in subsamples of women with different prepregnancy BMI categories (See Appendix C -Supplementary Table 2)

Supplementary Table 3 in Appendix C shows results of the longitudinal analysis using generalized estimating equations. Results are similar to our findings for the primary analysis. Compared to high breastfeeding intensity, low and medium breastfeeding intensities were associated with higher postpartum weight retention over time (β =3.4 lbs.; 95% CI: 1.6, 4.9 lbs.; β =2.1; 95% CI: 0.7, 4.0, respectively). Postpartum time remained a significantly negative predictor of postpartum weight retention (β = -0.2.; 95% CI: -0.3, -0.1). In addition, maternal caloric intake per 100 kcal was a significant positive predictor of postpartum weight retention (β = 0.3 lbs.; 95% CI: 0.1, 0.4). See Appendix C for Supplementary Table 3.

DISCUSSION AND CONCLUSIONS

The present study examined the relationship between breastfeeding practices and postpartum weight retention among US mothers using a longitudinal dataset. Our study found a significant negative relationship between breastfeeding intensity and postpartum weight retention at 12 months which is similar to findings from other studies.[106,191] Given recent findings that have established obesity as a significant risk factor for postpartum weight retention, and the significant interaction term, our multivariable linear regression results are presented by prepregnancy BMI. Our analyses showed that higher breastfeeding intensity and over 9-month breastfeeding duration resulted in significant lower postpartum weight retention at 12 months, but this association only remained among normal weight women when stratified by prepregnancy BMI. In our subanalysis of a smaller sample of women with information on postpartum caloric intake, we still found a significant association between categories of breastfeeding intensity and postpartum weight retention at 12 months. We no longer saw associations between categorical measures of breastfeeding duration and postpartum weight retention among all women However, when stratified by prepregnancy BMI we still found significant associations among normal weight women after adjusting for caloric intake. These discrepant results could have been due to reduction in sample size or additional control of maternal caloric intake.

A longitudinal study conducted by Kac et al. (n=405) among a cohort of Brazilian women followed up till 9 months postpartum did not find a significant association between breastfeeding duration and postpartum weight retention among obese women, but, did find a significant weight reduction among women with <30% body fat which is similar to normal weight women in our study.[191] Another prospective cohort study conducted by Baker et al. among a Danish cohort (n=36,030) found that breastfeeding was negatively associated with ≥ 5kg weight retention at 6 and 18 months postpartum among all categories of BMI except obese class II and III. In addition, a recent randomized clinical trial which assessed the impact of lifestyle interventions (diet and physical activity) among obese women found that breastfeeding duration >6 months was negatively associated with >5kg weight retention.[181] The lack of association seen among overweight and obese women in our study was partly explained by Kac et al. It was postulated that normal weight women have higher changes in their fat mass compared to overweight and obese women.[192] Therefore, leaner women tend to lose greater fat postpartum because of the higher changes in fat mass during pregnancy, and effects of breastfeeding may be limited among obese women.[191] Another hypothesis is that obese women prior to pregnancy may find it difficult to initiate breastfeeding and also have a lower duration of breastfeeding compared to normal weight women. [187,188]

A recent systematic review by Neville et al. concluded that there was insufficient evidence to suggest that breastfeeding promotes weight loss. The authors cited methodological issues (sample size, methods of assessing weight and infant feeding practices, not accounting for known confounders or effect modifiers e.g. prepregnancy BMI, parity, etc.) as a major factor that makes it difficult to compare findings from different studies. Although most of the reviewed studies showed no association between breastfeeding and weight change, 4 out of 5 studies considered to be of high quality showed a positive association between breastfeeding and postpartum weight change.[91] Our study accounted for some of the methodological issues by using a fairly large sample size and presenting our linear regression analysis by prepregnancy BMI. Another systematic review and meta-analysis paper of 11 studies showed evidence that breastfeeding duration for 3 to ≥ 6 months reduces postpartum weight retention but duration > 6 months seems not to have an influence on postpartum weight retention. On average, mothers who breastfed lost an average of 0.87 kg, i.e. 1.9 lbs. (95% CI: 0.57, 1.17kg) compared to mothers who formula-fed their offspring.[32]

It is assumed that breastfeeding should promote postpartum weight loss because of evidence of increased energy needs of breastfeeding mothers which is estimated to be about 2090 kj/day greater than their non-breastfeeding counterparts.[193] However, the causes of weight gain are multifactorial including maternal age, gestational weight gain, socioeconomic status, and other lifestyle behaviors. Two recent studies which assessed the impact of lifestyle behaviors on postpartum weight retention found different results. The first study which was conducted among pregnant women in Mexico (n=314) found that exclusive breastfeeding for 3 months was associated with a higher reduction in postpartum weight, but no association was found when assessing postpartum weight retention with physical activity and energy intake.[194] The second study which was conducted using data from the Danish National Birth Cohort (n=23,701) found that healthy diet (high intake of fruits, vegetable, fish, and poultry), more leisure-time exercise, low sedentary behaviors, and higher duration of breastfeeding were associated with reduced odds of gaining >5 kg at 7 years postpartum.[195] This suggests that intervention studies incorporating breastfeeding components with healthy lifestyle behavior may result in lower postpartum weight retention. Boghossian et al. examined the association between postpartum weight retention and dietary patterns, breastfeeding, and caloric intake using the same IFPS dataset (n=1136). Findings from the study showed that total energy intake and breastfeeding scores (intensity and duration) were significant predictors of postpartum weight retention at 12 months, although no association was seen between postpartum diet quality and postpartum weight retention. [196]

Despite guidelines for breastfeeding by the AAP and WHO, recent estimates showed that many US mothers are not meeting the recommended goals for exclusive breastfeeding.[186] Given other factors (cultural, socio-demographic, and obesity) influencing rates of breastfeeding, it may be more effective to address the underlying risk factors of low breastfeeding rates rather than simply encouraging women to breastfeed more. As discussed by Neville et al., there may be other factors which may affect mothers who breastfeed differently such as duration and quality of sleep, stress associated with establishing feeding routines, and psychological health.[2] All these may have implications for weight gain among women.

Our study has some limitations which must be discussed. The IFPS II data is not nationally representative and consists of mostly white, educated, and higher socioeconomic status women, which may limit the generalizability of our findings. Second, all information was self-reported by mothers, and there was no objective assessment of maternal weight measurements. This could have led to non-differential misclassification bias from women underreporting their weight and would have biased our results towards the null. Moreover, any bias resulting from women underreporting their prepregnancy weights would be very similar to the bias resulting from the reporting of the postpartum weight; therefore the difference between the two weights should not be biased.[197,198] Third, sample attrition in the survey was high with the response rates at the 12-month questionnaire approximately 63%. Findings showed that that those who dropped out of the study were more likely to be younger, nonwhite, women of lower socioeconomic status and lower educational level, and live in the southern region of the country.[178] It is possible that women who completed the study have more health seeking behaviors due to their higher educational level. However, the potential selection bias resulting from sample attrition may not be an issue in a longitudinal prospective study because for bias to occur, selection of participants must be related to both exposure and outcome. In this scenario, participants are not aware of the outcome of the study and have not experienced it. Although retention in the IFPS II survey may be related to the exposure, it was not related to our outcome of interest, therefore the influence of selection bias in our study would be nonsignificant. Fourth, there was no information on mothers' physical activity level, which is a known factor influencing weight gain.[181,194,195] It is possible that mothers who breastfeed more or for longer periods are more health conscious and may have other health-seeking behaviors.[199] Finally, we could only control for caloric intake in a smaller sample of women. Future studies should further verify the association in a large sample of women, which would allow for stratified analysis by mother's pre-pregnancy weight.

Despite the above-mentioned limitations, our study has some unique strengths. A major strength is the prospective longitudinal study design with extensive information on infant feeding practices throughout the first year of life. The relatively large sample size in comparison to other studies, increased our statistical power to detect an association between our variables of interest. Lastly, breastfeeding measures were assessed multiple times which may have limited recall bias in exposure assessment and gave us the ability to analyze two different measures of breastfeeding (intensity and duration).

In conclusion, high breastfeeding intensity during the first 6 months of infancy and longer breastfeeding duration were associated with reduction in postpartum weight at 12 months and weight change at 6, 9, and 12 months. Given high rates of overweight and obesity among reproductive age women in the US and the complications associated with excessive weight, our findings are of public health importance. Previous studies on lifestyle intervention were focused on lifestyle factors such as physical activity and diet, and fewer studies have added breastfeeding components. Given the multifactorial causes of weight gain among women, promoting breastfeeding in association with healthy lifestyle behavior may be an effective method to reduce pregnancy-related weight retention.

Table 6.1: Descriptive Sample Characteristics of the Infant Feeding Practices Survey II according to Breastfeeding Intensity Categories during the first 6 months

Variables	Breastfeeding Intensity				
	Total	**Low (>20%)**	**Medium (20-80%)**	**High (>80%)**	P-value
Total n (%)	1287 (100.0)	447 (34.7)	215 (16.7)	625 (48.6)	
Maternal age in years, mean (SD)	30.3 (5.1)	29.8 (5.6)	30.8 (5.4)	30.4(4.7)	0.065
Maternal education					**<0.0001**
High school or less	215 (16.7)	122 (27.3)	28 (13.0)	65 (10.4)	
Some College	449 (34.9)	168 (37.6)	82 (38.1)	199 (31.8)	
College graduate	449 (34.9)	116 (25.9)	78 (36.3)	255 (40.8)	
Post Graduate	174 (13.5)	41 (9.2)	27 (12.6)	106 (17.0)	
Race					**0.003**
White	1136 (88.2)	389 (87.0)	178 (82.8)	569 (91.0)	
Non-white	151 (11.8)	58 (13.0)	37 (17.2)	56 (9.0)	
Poverty income Ratio					**0.052**
≤185%	452 (35.1)	175 (39.2)	60 (27.9)	217 (34.7)	
>186-300%	347 (27.0)	108 (24.2)	63 (29.3)	176 (28.2)	
≥300%	488 (37.9)	164 (36.7)	93 (42.8)	232 (37.1)	
Marital status					**<0.0001**
Married	1088 (84.5)	341 (76.3)	177 (82.3)	570 (91.2)	
Not married	199 (15.5)	106 (23.7)	38 (17.7)	55 (8.8)	
Nulliparous					**<0.0001**
Yes	345 (26.8)	144 (32.2)	70 (32.6)	131 (21.0)	
No	942 (73.2)	303 (67.8)	145 (67.4)	494 (79.4)	
Postpartum Smoking					**<0.0001**
Yes	224 (17.4)	139 (31.1)	39 (18.1)	46 (7.4)	
No	1063 (82.6)	308 (68.9)	176 (81.9)	579 (92.6)	

Prepregnancy BMI					**0.0003**
Normal	645 (50.1)	191 (42.7)	110 (51.2)	344 (55.0)	
Overweight	326 (25.3)	110 (24.5)	57 (26.5)	159 (25.5)	
Obese	316 (24.6)	146 (32.7)	48 (22.3)	122 (19.5)	
Met IOM recommendations for gestational weight gain					0.417
Inadequate	198 (15.4)	71 (15.9)	35 (16.3)	92 (14.7)	
Adequate	488 (37.9)	155 (34.7)	80 (37.2)	253 (40.5)	
Excessive	601 (46.7)	221 (49.4)	100 (46.5)	280 (44.8)	
Method of delivery					**0.013**
Vaginal	919 (71.4)	298 (66.7)	156 (72.6)	465 (74.4)	
Caesarean	368 (28.6)	149 (33.3)	59 (27.4)	160 (25.6)	
Breastfeeding duration (month), mean (SD)	7.4 (5.4)	0.9 (1.4)	6.2 (3.1)	12.2 (2.2)	**<0.0001**

* No breastfeeding group was included in the low intensity group

Statistical tests by chi-square for categorical variables and ANOVA for continuous variables.

Table 6.2. Mean maternal weight retention at 12 months according to breastfeeding intensity in the first 6 months of life, stratified by mother's prepregnancy BMI

	Low breastfeeding intensity (>20%)		Medium breastfeeding intensity (20-80%)		High breastfeeding intensity (>80%)		P-value*
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
All women (n=1287)	447	4.0(17.8)	215	3.5 (16.1)	625	1.7 (13.9)	0.047
Normal weight (n=645)	191	7.6 (16.7)	110	5.2 (10.3)	344	2.7 (10.9)	<0.0001
Overweight (n=326)	110	4.2 (13.3)	57	5.4 (17.0)	159	2.7 (13.7)	0.399
Obese (n=316)	146	-1.0 (19.2)	48	-3.3 (22.7)	122	-2.3 (19.8)	0.756

* Statistical tests by ANOVA with significance set at p <0.05

Table 6.3. Adjusted analysis between breastfeeding intensity and weight retention at 12 months, stratified by prepregnancy BMI

Breastfeeding measures	All women* (n=1287) β (95% CI) P-value	Normal weight (n= 645) β (95% CI) P-value	Overweight (n= 326) β (95% CI) P-value	Obese (n=316) β (95% CI) P-value
Breastfeeding intensity				
Low (<20%)	3.6 (1.5, 5.6) 0.001	4.5 (2.1, 6.9) 0.0003	1.4 (-2.3, 4.8) 0.463	2.7(-2.9, 8.3) 0.338
Medium (20-80%)	2.6 (1.0, 5.1) 0.047	2.8 (0.1, 5.6) 0.049	2.3 (-1.8, 6.9) 0.288	2.3(-5.2, 9.9) 0.548
High (≥ 80%)	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference
Breastfeeding duration (per 1-week increase)	-0.08 (-0.1, -0.03) 0.0003	-0.09 (-0.14, -0.05) 0.002	-0.01 (-0.09, 0.06) 0.707	-0.08 (-0.20, 0.03) 0.166
Breastfeeding duration				
>0 to < 3 months	4.5 (2.8, 6.9) 0.0002	6.5 (3.6, 9.4) <0.001	-0.01 (-4.4, 4.2) 0.997	5.1 (-1.3, 11.4) 0.120
3 to <6 months	3.3 (-0.1, 5.6) 0.056	2.1 (-1.4, 5.6) 0.240	3.38 (-2.2,9.9) 0.236	4.3 (-4.2, 12.8) 0.320
6 to < 9 months	2.9 (0.1, 5.8) 0.042	3.6 (0.2, 7.0) 0.040	-0.01 (-4.9, 4.7) 0.354	6.9 (-1.5, 15.3) 0.108
≥ 9 months	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference

Adjusted for maternal age, education, parity, gestational weight gain, income, marital status, and postpartum smoking
* Additionally, adjusted for prepregnancy BMI
β = weight retention in lbs

Table 6.4. Association between breastfeeding intensity and postpartum weight retention in the IFPSII cohort using generalized estimating equations (n=1692)

	Weight retention (lbs.)	
Variables	β (95% CI)	P-value
Postpartum time	-0.3 (-0.3, -0.11)	<0.001
Breastfeeding intensity		
Low (<20%)	3.4 (1.6-4.9)	0.001
Medium (20-80%)	2.1 (0.7-4.0)	0.041
High (>80%)	1.0 ref	
Maternal age (1-year increase)	-0.1(-0.3-0.1)	0.134
Maternal education		
Less than or High school	3.6 (1.5, 6.6)	0.011
Some college	1.3 (-1.1, 3.7)	0.356
College	1.2 (-0.8, 3.0)	0.384
Post Graduate	1.0 ref	
Postpartum smoking		
No	3.3 (0.7, 5.9)	0.012
Yes	1.0 ref	
Poverty income ratio		
≤185%	1.9 (0.01, 3.8)	0.049
>186-300%	1.6 (-0.7, 3.3)	0.058
≥300%	1.0 ref	
Nulliparous		
Yes	-1.2 (-2.9, 0.5)	0.162
No	1.0 ref	
Prepregnancy BMI		
Overweight	-3.5 (-5.1, -1.9)	<0.0001
Obese	-9.6 (-11.7, -7.4)	<0.0001
Normal weight	1.0 ref	
Married		
No	2.1 (-0.5, 4.7)	0.103
Yes	1.0 ref	

Adjusted for postpartum time, maternal age, education, parity, postpartum smoking income, prepregnancy BMI, and marital status

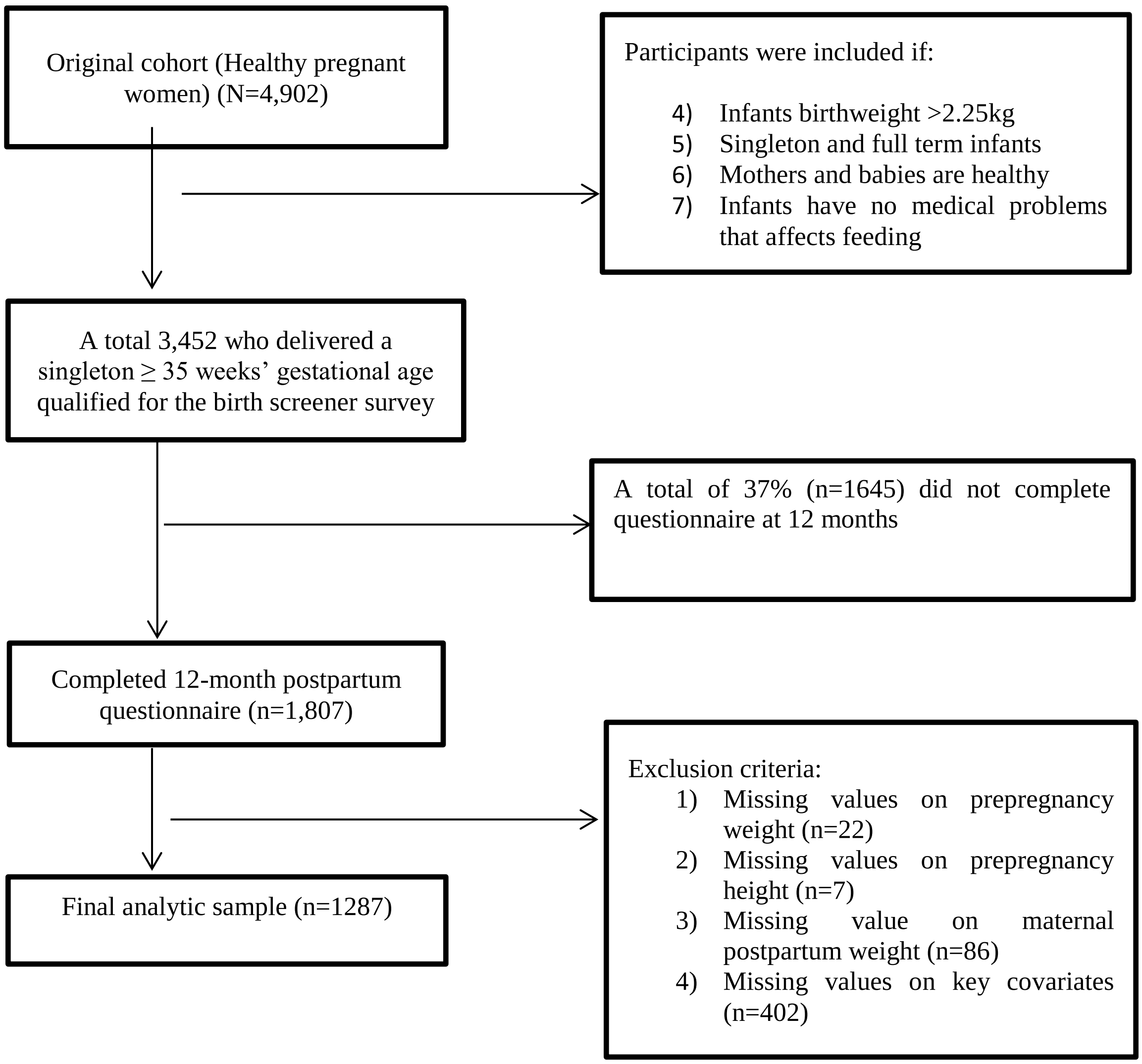

Figure 6.1 Flow Chart of Study Participants for Aim 3

CHAPTER 7

SUMMARY AND CONCLUSIONS

The overall aim of this dissertation was to identify early life factors influencing health in children and mothers in the US and China. Specifically, we assessed 1) the relationship between maternal gestational weight gain and offspring weight at 1 year in rural China while examining the mediating role of birth weight; 2) the association between breastfeeding practices and allergic conditions and asthma at 6 years among a cohort of US 6-year-old; and 3) the relationship between breastfeeding practices and postpartum weight retention at 12 months and maternal weight changes at 6, 9, and 12 months postpartum. Study1 used data from a recent prospective study from a Chinese cohort, while Studies 2 use data from the Infant Feeding Practice Survey II and its 6-year follow-up survey conducted by the Centers for Disease Control and Prevention and the US Food and Drug Administration. Lastly, Study 3 used data from the Infant Feeding Practice Survey II only.

Key Findings

In Study 1, inadequate gestational weight gain was more prevalent (51%) than excessive gestational weight gain and adequate gestational weight gain in this rural community located in the Southwest China. However, despite the low rate of excessive gestational weight gain in rural China, there was still a positive association between maternal gestational weight gain and offspring weight-for–age Z-score at 1 year. Second, we found that birth weight was a significant mediator (32.9% mediated) in this relationship. Our linear regression analysis did not find significant associations between GWG measures and weight-for-length Z scores. Important correlates of GWG in rural China were maternal occupation and ethnicity.

The second study used the data from the IFPS II and its Y6FU and examined the association between breastfeeding practices and allergic conditions. Although we found a two-fold increased risk of skin allergy/eczema among children who were not exclusively breastfed when compared with children who were exclusively breastfed for at least 4 months, this finding may be due to chance since there was no dose -response effect seen. In addition, we did not find any association between the duration of breastfeeding and allergic conditions and asthma at 6 years. The major risk factor for allergic conditions and asthma among children in this cohort was positive history infantile eczema.

In Study 3, high breastfeeding intensity (defined as the number of milk feedings that are breast milk) during the first 6 months of infancy and higher breastfeeding duration was associated with a reduction in postpartum weight at 12 months and weight change at 6, 9, and 12 months. When compared with high breastfeeding intensity, low breastfeeding and medium breastfeeding had a higher postpartum weight retention ($\beta=3.6$, $p=0.003$; $\beta=2.6$ $p=0.047$, respectively). Although this association remained significant among normal weight women alone, our inability to see significant association among overweight and obese women may be due to lack of power due to the smaller sample size in these categories of BMI. Patterns of breastfeeding intensity differ by maternal education, income, parity, maternal smoking, and methods of delivery, and

marital status. Specifically, married women, multiparous, non-smoker, those with a college degree, and those who delivered vaginally had higher breastfeeding intensity.

Public Health Implications of Dissertation

Findings from this dissertation are of public health significance both in the developing and developed countries. Given high rates of childhood obesity worldwide, our finding of an association between maternal gestational weight gain and offspring weight-for-age Z scores despite low rates of excessive gestational weight gain is relevant in an area where this association was understudied. There are still gaps in knowledge in our understanding of the relationship between maternal GWG and offspring weight in rural China. To our knowledge, this is the first study that examined the relationship using advanced statistical method (mediation analysis) to tease out the direct and indirect effect of GWG on offspring weight, and this gave us preliminary insight into the impact of a mediator on what we previously thought was a direct and straightforward association. In addition, the higher prevalence of inadequate GWG among women in rural China suggests the need for interventions that would promote healthy nutrition and optimal weight gain for mothers and offspring.

Our findings are also important for child health in terms of preventing childhood obesity and its associated adverse health outcomes. Childhood obesity is known to be associated with weight gain later in life, which has significant health implications. Obesity is a well-established risk factor for heart disease, stroke, type II diabetes mellitus, and cancers. Therefore, efforts should be made to promote healthy weight gain in infants. Our findings add to the body of knowledge of the importance of healthy gestational weight gain on offspring's weight in rural China. Public health practitioners and policymakers can incorporate healthy lifestyle behaviors into interventions programs to promote optimal weight gain before and during pregnancy among mothers, which can help promote healthy weight gain in the offspring in the early life.

Although, our second study found an association between non-exclusive breastfeeding and skin allergy, when compared with exclusive breastfeeding >4 months, it is important to note that this finding may be due to chance because of the lack of a dose-response effect i.e. no association seen among children who were never breastfed compared with the reference group. In addition, we did not find any association between breastfeeding (exclusivity and duration) and hay fever and asthma. Despite these findings, this study allowed us to provide a detailed assessment of this relationship using recent data of US mothers and their offspring. In addition, we also saw recent estimates of breastfeeding rates among US mothers, which is relevant because of other established benefits of breastfeeding on offspring. The association between breastfeeding and allergic conditions has been controversial over the past decades. Because of the unique nature of our data (less racially diverse dataset), we were not able to adequately capture the impact of race, a well-known confounder in this association. Despite the paucity of an association between breastfeeding and allergic conditions, mothers should be encouraged to breastfeed their children given other benefits of breastfeeding. However, this association should be examined critically among high-risk children (prior history of eczema, and family history of eczema) using data generalizable to the US population.

The third study, examining the relationship between breastfeeding and postpartum weight retention using a longitudinal prospective data, found significant associations. This finding is of public health significance given high rates of obesity among reproductive-age women. As discussed earlier, postpartum weight retention is a known predisposing factor for obesity. Therefore, preventing obesity by reducing postpartum weight retention can be an effective intervention strategy for obesity prevention among women of reproductive age group. Breastfeeding has the promise of helping women to reduce weight retention postpartum. Apart from both short-term and long-term complications associated with obesity, it is also a major cause of high health care expenditure and economic burden in the United States. Our findings are also of clinical relevance because obesity is a known risk factor for chronic health conditions, and efforts should be made to promote healthy weight among women. Promoting healthy lifestyle behavior in combination with breastfeeding may be an effective intervention among women.

In conclusion, the findings from this dissertation filled some gaps in existing literature by using recent data and advanced statistical methods to highlight maternal and child health outcomes, of both public health and clinical significance. Findings could be helpful for public health practitioners to design health programs to improve maternal and child health both in the US and worldwide.

Future Research

Future research should aim to expand upon these dissertation findings by replicating these findings using a generalizable study population. Specifically, study 1 should be replicated using a larger sample and assess the mediating role of birth weight in the relationship between GWG and offspring weight in later years (e.g. 3 and 5 years). This would enable us to assess if the mediating role of birth weight persists over time and add to the body of knowledge in maternal and child health. Other future research should also examine this relationship in other developing countries to see if our understanding of gestational weight gain in these areas differs from what was previously known. To the best of our knowledge, this is the first study conducted in rural China using advanced statistical methods. Given that almost 60% of the Chinese population lives in rural China, [132] more studies are needed in rural population.

The study population in studies 2 and 3 consisted of mostly white, educated and middle-income women and is not generalizable to the US population which is more diverse. Future studies should be replicated using a more generalizable study sample. This would provide a better understanding of racial disparities in breastfeeding rates, disparities in allergic conditions, and the role of sociodemographic characteristics in these associations. In study 2, assessment of allergic conditions was via mother's self-report, which was not validated using medical records. Future research should focus on ensuring objective assessment of allergies such as skin allergen test, blood testing, and medical chart review.

The significant results observed in Study 3 further points to the need for more lifestyle behavior intervention studies that would incorporate a breastfeeding component. This may be a more effective strategy to reduce excessive weight gain during pregnancy and the postpartum period.

Conclusions

This dissertation utilized advanced statistical methods to examine relevant maternal and child health issues both in China and the United States. Results from this dissertation gave us a better understanding of weight gain in a developing country and helped us understand the beneficial effect of breastfeeding on other less established maternal outcome such as postpartum weight retention. Encouraging women to gain healthy weight during pregnancy is still relevant in the developing world. The results from the dissertation are also useful for women to be more conscious of weight gain during pregnancy and are important for health providers to individualize preconception or prenatal care to women about their weight gain during pregnancy. In addition, it would also help public health practitioners assess, design and promote more effective healthy nutrition programs that may further improve maternal and child health outcomes.

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APPENDIX A: SUPPLEMENTARY TABLES ASSOCIATED WITH CHAPTER 4

SUPPLEMENTARY TABLE 1. Crude and adjusted analysis between adequacy of GWG (using WHO BMI cut-off point and IOM guidelines) and weight-for-age Z-scores and weight-for-length Z scores.

	Weight-for-age Z scores		**Weight-for-Length Z scores**	
	Crude	**Adjusted [a]**	**Crude**	**Adjusted [a]**
	β (95% CI) **P-value**	**β (95% CI)** **P-value**	**β (95% CI)** **P-value**	**β (95% CI)** **P-value**
GWG categories [b]				
Inadequate vs. adequate	-0.24 (-0.45, -0.03) **0.029**	-0.23 (-0.45, -0.01) **0.041**	-0.21(-0.45, 0.00) 0.051 [c]	-0.19 (-0.41, 0.00) 0.091 [c]
Excessive vs. adequate	0.08 (-0.19, 0.34) 0.545	0.06 (-0.22, 0.33) 0.689	0.09 (-0.19, 0.34 0.539	0.06 (-0.21, 0.33) 0.658
Gestational age (per 1-week increase)		0.07 (-0.01, 0.15) 0.092		0.07 (-0.01, 0.15) 0.079
Age at parturition (per 1-yr increase)		-0.001 (-0.02, 0.02) 0.899		-0.001 (-0.02, 0.01) 0.903
Ethnicity				
Zhuang versus others		-0.27 (-0.56, 0.01) 0.060 [c]		-0.28 (-0.56, 0.01) 0.056 [c]
Mother's occupation				
Farmers vs. non-farmers		-0.31 (-0.52, -0.09) **0.006**		-0.29 (-0.51, -0.08) **0.007**
Offspring sex				
Female versus male		0.03 (-0.16, 0.21) 0.770		-0.01 (-0.19, 0.18) 0.958

	-0.28 (-0.66, 0.09)	
Pregnancy Complication	0.132	-0.33 (-0.70, 0.04)
Yes vs. No		0.083[c]

[a] Adjusted for maternal age, gestational age, ethnicity, occupation, pregnancy complication, and offspring's sex

[b] Prepregnancy BMI used to calculate GWG categories: underweight (<18.5 kg/m^2), normal weight (≥18.5-25.9 kg/m^2), overweight (25.0-25.9 kg/m^2, and obese (≥30.0 kg/m^2).

[c] Borderline significance p <0.1

SUPPLEMENTARY TABLE 2. Crude and adjusted analysis between adequacy of GWG (Asian BMI cut-off point and IOM guidelines) and weight-for-age Z-scores and weight-for-length Z scores

	Weight-for-age Z scores		**Weight-for-Length Z scores**	
	Crude	**Adjusted [a]**	**Crude**	**Adjusted [a]**
	β (95% CI) **P-value**	**β (95% CI)** **P-value**	**β (95% CI)** **P-value**	**β (95% CI)** **P-value**
GWG categories [b]				
Inadequate vs. adequate	-0.24 (-0.45, -0.02) **0.031**	-0.21 (-0.43, 0.00) 0.053[c]	-0.20 (-0.49, -0.15) 0.061[c]	-0.17 (-0.38, 0.05) 0.121
Excessive vs. adequate	0.17 (-0.10, 0.42) 0.213	0.15 (-0.11, 0.41) 0.689	0. 16 (-0.11, 0.42) 0.241	0.15 (-0.11, 0.41) 0.262
Gestational age (per 1-week increase)		0.07 (-0.01, 0.15) 0.092		0.07 (-0.01, 0.15) 0.073[c]
Age at parturition (per 1-yr increase)		-0.001 (-0.02, 0.02) 0.939		-0.001 (-0.02, 0.01) 0.818
Ethnicity				
Zhuang vs. others		-0.28 (-0.56, 0.00) 0.060[c]		-0.28 (-0.56, -0.00) **0.049**
Mother’s occupation				
Farmers vs non-farmers		-0.29 (-0.50, -0.08) **0.008**		-0.28 (-0.49, -0.07) **0.009**
Offspring sex				
Female versus male		0.02 (-0.16, 0.20) 0.834		-0.01 (-0.19, 0.18) 0.903
Pregnancy Complication				
Yes vs. No		-0.30 (-0.67, 0.08) 0.118		-0.33 (-0.70, 0.04) 0.076[c]

[a] Adjusted for maternal age, gestational age, ethnicity, occupation, pregnancy complication, and offspring's sex

[b] Prepregnancy BMI used to calculate GWG categories: underweight (<18.5 kg/m^2), normal weight (≥18.5-22.99 kg/m^2), overweight (23-27.49 kg/m^2, and obese (≥27.5 kg/m^2).
[c] Borderline significance $p < 0.1$

APPENDIX B: SUPPLEMENTARY TABLE ASSOCIATED WITH CHAPTER 5

SUPPLEMENTARY TABLE 1. Adjusted Odds Ratio for Allergic Disorders and Asthma According to Exclusivity of Breastfeeding among Children without Infantile Eczema (N=998)

	Odds Ratio (OR) and 95% Confidence Interval	
Variables	**Model 1**	**Model 2**
Eczema / Skin allergy		
No breastfeeding	0.7 (0.3-2.1)	0.6 (0.2-1.9)
Breastfeeding, but no exclusivity	**2.0 (1.0- 4.0)**	1.7 (0.8-3.6)
Exclusive breastfeeding < 4 months	1.0 (0.4-2.3)	0.9 (0.4-2.1)
Exclusive breastfeeding ≥ 4 months	1.0 Reference	1.0 Reference
Hay Fever/ Respiratory Allergy		
No breastfeeding	1.1 (0.6-2.1)	1.0 (0.5-2.1)
Breastfeeding, but no exclusivity	1.3 (0.8-2.2)	1.2 (0.7-2.1)
Exclusive breastfeeding < 4 months	0.9 (0.5-1.6)	0.7 (0.4-1.4)
Exclusive breastfeeding ≥ 4 months	1.0 Reference	1.0 Reference
Asthma		
No breastfeeding	1.1 (0.3- 3.1)	1.3 (0.4-4.0)
Breastfeeding, but no exclusivity	1.4 (0.6-3.2)	1.5 (0.6-3.5)
Exclusive breastfeeding < 4 months	0.8 (0.3-2.1)	0.9 (0.3-2.3)
Exclusive breastfeeding ≥ 4 months	1.0 Reference	1.0 Reference

Model 1: Unadjusted

Model 2: Adjusted for maternal race, education, income, method of delivery, maternal smoking status, parity, age of solid food introduction, family history of allergy and child’s sex

APPENDIX C: SUPPLEMENTARY TABLES ASSOCIATED WITH CHAPTER 6

SUPPLEMENTARY TABLE 1. Association between breastfeeding intensity and postpartum weight retention in the IFPSII cohort using generalized estimating equations using full sample (n=1692)

	Weight retention (lbs.)	
Variables	β (95% CI)	P-value
Postpartum time	-0.2 (-0.3, -0.1)	<0.001
Breastfeeding intensity		
Low (<20%) vs. high	3.8 (2.1, 5.5)	0.001
Medium (20-80%) vs. high	2.7 (0.8, 4.7)	0.006
High (>80%)	1.0 ref	
Maternal age (1-year increase)	-0.1(-0.3, 0.1)	0.507
Maternal education		
Less than or High school	3.4 (1.3, 6.1)	0.012
Some college	0.5 (-1.7, 2.7)	0.664
College	0.5 (-1.3, 2.4)	0.585
Postgraduate	1.0 ref	
Postpartum smoking		
No	2.7 (0.5, 5.4)	0.039
Yes	1.0 ref	
Poverty income ratio		
≤185% vs.	2.2 (0.3,4.0)	0.026
>186-300%	1.2 (-0.7, 2.8)	0.168
≥300%	1.0 ref	
Nulliparous		
Yes	-1.1 (-2.9, 0.7)	0.223
No	1.0 ref	
Prepregnancy BMI		
Overweight	-3.2 (-4.8, -1.6)	<0.001
Obese	-9.5 (-11.7, -7.3)	<0.001
Normal weight	1.0 ref	
Marital status		
No	2.7 (0.3, 5.1)	0.030
Yes	1.0 Ref	

Adjusted for postpartum time, maternal age, education, parity, postpartum smoking income, prepregnancy BMI

SUPPLEMENTARY TABLE 2. Adjusted analysis between breastfeeding intensity and weight retention at 12 months, stratified by prepregnancy BMI

	All women* (n=871)	Normal weight (n= 440)	Overweight (n= 224)	Obese (n=206)
Breastfeeding measures	β (95% CI) P-value	β (95% CI) P-value	β (95% CI) P-value	β (95% CI) P-value
Breastfeeding intensity				
Low (<20%)	2.7 (0.1, 5.3) 0.043	2.7 (-0.5, 5.9) 0.094†	2.1 (-2.9, 7.1) 0.408	1.2 (-6.1, 8.3) 0.752
Medium (20-80%)	3.1 (1.0, 6.1) 0.043	4.3 (0.9, 7.8) 0.014	1.5 (-4.2, 7.4) 0.589	2.6 (-6.5, 11.7) 0.560
High (≥ 80%)	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference
Breastfeeding duration (per 1-week increase)	-0.05 (-0.1, -0.00) 0.060†	-0.04 (-0.1, -0.02) 0.183	-0.03 (-0.09, 0.06) 0.629	-0.01 (-0.16, 0.13) 0.166
Breastfeeding duration				
>0 to < 3 months	2.8 (-0.3, 5.9) 0.078†	3.2 (-0.7, 7.0) 0.011	1.2 (-4.9, 7.4) 0.693	1.4 (-6.7, 9.7) 0.727
3 to <6 months	1.8 (-1.8, 5.5) 0.333	2.0 (-2.4, 6.5) 0.387	1.6 (-5.6, 8.8) 0.656	-0.2 (-10.4, 9.9) 0.963
6 to < 9 months	1.7 (-1.7, 5.1) 0.338	2.6 (-1.4, 6.7) 0.208	-0.6 (-6.9, 5.8) 0.867	-1.8 (-12.3, 8.75) 0.738
≥ 9 months	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference

Adjusted for maternal age, education, parity, gestational weight gain, income, marital status, postpartum smoking, and caloric intake
* Additionally, adjusted for prepregnancy BMI
† Borderline significance
β = weight retention in lbs.

SUPPLEMENTARY TABLE 3. Association between breastfeeding intensity and postpartum weight retention in the IFPSII cohort using generalized estimating equations (n=1389)

	Weight retention (lbs.)	
Variables	β (95% CI)	P-value
Postpartum time	-0.3 (-0.4, -0.1)	<0.001
Breastfeeding intensity		
Low (<20%)	3.3 (1.1, 5.4)	0.001
Medium (20-80%)	2.8 (0.6, 5.2)	0.015
High (>80%)	1.0 ref	
Maternal age (1-year increase)	0.35 (-0.3-0.1)	<0.001
Maternal education		
Less than or High school	3.4 (0.2, 6.6)	0.038
Some college	-0.3 (-2.9, 2.3)	0.817
College	-0.5 (-2.7, 1.8	0.693
Post Graduate	1.0 ref	
Postpartum smoking		
No	2.1 (-0.5, 4.9)	0.124
Yes	1.0 ref	
Poverty income ratio		
≤185%	1.9 (0.01, 3.8)	0.049
>186-300%	1.6 (-0.7, 3.3)	0.058
≥300%	1.0 ref	
Nulliparous		
Yes	-0.2 (-1.8, 2.2)	0.828
No	1.0 ref	
Prepregnancy BMI		
Overweight	-1.1 (-3.5, 1.3)	0.375
Obese	-4.0 (-7.2, -0.7)	0.015
Normal weight	1.0 ref	
Married		
No	3.4 (0.4, 6.3)	0.023
Yes	1.0 ref	
Caloric Intake (per 100-kcal increase	0.003 (0.001, 0.004)	<0.001