ABSTRACT

Title: GESTATIONAL WEIGHT GAIN, INFANT FEEDING PRACTICES, AND INFANT GROWTH

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Suboptimal growth is apparent across generations. Gestational weight gain (GWG) and infant feeding have been linked to child growth trajectories. This study assessed the joint association of GWG and infant feeding with three growth outcomes: length, weight, and weight-for-length.

I analyzed data from the Infant Feeding Practices Study II (2007), a nationally-based sample of mother/infant dyads followed from the third trimester of pregnancy through infancy (N=1939). GWG was defined as inadequate, adequate, and excessive. Predominant feeding categories were defined as ≥ 70% breast fed, ≥ 70% formula fed, and mixed fed. Linear multiple regression and mixed effect models were fit to achieve the study aims.

At three months, compared to the adequate GWG group, the inadequate group were lighter (-0.24 lbs.; 95% CI: -0.36, -0.12) and shorter (-0.13 in.; 95% CI: -0.23, -0.03), while the excessive group was heavier (0.28 lbs.; CI: 0.19, 0.38) and longer (0.09 in.; 95% CI: 0.01, 0.17). At five months, compared to breastfed infants, formula fed infants were heavier (0.38 lbs.; 95% CI: 0.26, 0.50); and the association between feeding type and length was apparent at seven months, where formula fed were longer (0.24 in.; 95% CI: 0.10, 0.39). An association between feeding type and weight-for-length was evident at twelve months, where the ratio for formula fed was greater (0.03 lbs./in.; 95% CI: 0.03, 0.04). The weight gain trajectory of breastfed infants was lower than the other feeding groups. The length trajectories were highest among formula fed compared to breastfed and mixed fed infants. The interaction between GWG and feeding type was significant for weight ($p<0.05$) and marginally significant for length ($p=0.06$).

My findings suggest existence of a difference in growth by GWG and feeding type. The weight trajectory of breastfed infants is steadier than that of other infants, highlighting the protective effect of breastfeeding on excessive weight gain. The growth rate for all feeding groups was fastest between 3-5 months, suggesting a critical window for growth during early infancy. Interventions targeting pregnancy and infancy can influence growth trajectories and contribute to a shift in intergenerational population growth trends.

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Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, College Park in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2014

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Acknowledgements

I would like to extend my gratitude to those who have supported and encouraged me throughout this process. Foremost, I would like to thank my dissertation chair, Dr. Edmond Shenassa, for inspiring me to live up to my full potential. I would also like to thank Dr. Xin He for providing the guidance needed to conduct advanced analytic techniques. Dr. Stephanie Grutzmacher, for encouraging me to consider alternative approaches to achieve my dissertation goals. Dr. Ken Schoendorf for providing the necessary clinical perspective to ensure the relevancy of my research. Dr. Nadine Sahyoun for her epidemiologic expertise and thoughtful input. I would also like to extend my deepest gratitude to my husband, Andrew DiBari, for his unconditional love while I pursued this challenging academic feat. Last but not least, I will always be grateful for my parents, John and Kathy Sapienza, and my sister, Whitney Sapienza; for their love, support, and encouragement.

Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction

Overview:

Pregnancy and early infancy have a major influence on an infant's growth and overall health. The pregnancy period is a sensitive phase of development where a suboptimal maternal-fetal environment can disrupt the fetal growth trajectory, negatively impact the health of the fetus, and implicate the health of the infant post-birth as well. Survival during infancy (i.e., the first year of life) depends on an infant's ability to achieve developmental milestones, one of which is to maintain adequate growth.[1] Beyond survival, physical, motor, sensory, and perceptual development are also dependent on adequate growth. In short, growth is essential for functioning, viability, and to sustain a high quality of life.[1] Foremost, experiences during pregnancy have been linked to infant and child growth trajectories; suggesting that these patterns may have developmental origins.[2] A focus on the developmental origins of disease is necessary to develop early interventions and improve child health outcomes.

There is a growing consensus among researchers, policymakers, and healthcare providers that to better address children's health needs, we must focus research on early life experiences, in particular growth.[3] Suboptimal growth before the age of one can result in a multitude of poor child health outcomes and influence later health and overall quality of life.[4] Both slow and rapid growth can result in serious health consequences. For these reasons, infant growth is often used as an indicator of the overall health of a population.[5]

Growth processes:

Growth is a multifactorial phenomenon embedded within the larger context of health and human development. Although growth is highly correlated with hereditary factors, its variability among individual children has underlying modifiable determinants.[6,7] Growth-related processes begin at conception. After fertilization, the egg and sperm travel to the uterus where the cells differentiate to form the embryo and the placenta.[8] During the first trimester, major organ systems such as the brain, spinal cord, heart, and lungs, begin to form and become interconnected.[9] By the second trimester, bone and muscle growth are apparent as well.[10] During this period, the fetus starts to develop limbs, has a distinct human appearance, and gains the ability to see and hear.[11] During the third trimester, organs mature at a rapid pace to enable the fetus to survive outside the womb.[11] Although technological advancements have facilitated the monitoring of fetal development, birth weight and size are often used as a proxy to evaluate fetal growth processes. Ultimately, adequate fetal growth is essential for healthy infant growth and development.

Growth processes are responsible for a shift from complete dependency to later autonomy.[12] Infants gain on average 5-7 ounces per week in the first month and approximately 3 ounces per week through 12 months of age.[13] At birth, the head is disproportionately larger than the body. As a result, infants have limited muscle control and require constant support. Eventually, infants are able to roll, sit-up, prop themself up, crawl, and walk.[12] These milestones are dependent on an infants' ability to meet age-specific growth targets.[14] There are many factors in both the intrauterine and post-birth environments that contribute to growth processes. Two of the arguably more important determinants are gestational weight gain (GWG) and infant feeding practices.

Determinants of growth

Gestational weight gain:

Adequate fetal growth is predicated in part on maternal GWG, as the mother is the fetus' sole source of nutrition. The degree of GWG is dependent on a number of maternal characteristics such as pre-pregnancy body mass index (BMI), maternal diet, and metabolism.[15] These maternal characteristics impact fetal nutrient availability thereby influencing fetal growth.[16–19] In turn, GWG is best considered within the context of maternal pre-pregnancy BMI.

Healthy People 2020 (MICH-13, MICH-16.5) aims to increase the proportion of women delivering a live birth who had a healthy weight prior to pregnancy and reduce the proportion of adults who are obese.[20,21] In addition, the Institute of Medicine (IOM) recommends optimal weight gain based on pre-pregnancy body mass index (BMI) to improve the likelihood of positive birth outcomes.[22,15] Suboptimal maternal weight at conception impacts placental, embryonic, and fetal growth and increases the risk for pregnancy complications.[8] Inadequate GWG deprives the fetus of essential nutrients thereby increasing the risk of low birth weight (LBW), preterm birth, and infant mortality.[23,24] Furthermore, excessive GWG increases the risk of infants born large for gestational age (LGA).[8] GWG has a direct impact on fetal growth, birth outcomes, and infant growth post-birth.[25,26,27]

Infant feeding:

Breastfeeding is considered the gold standard for infant nutrition and as such has been promoted at both the national and international levels.[28,29] The American Academy of Pediatrics (AAP) and the U.S. Surgeon General emphasize the importance of exclusive breastfeeding for six months and as a nutritional supplement through one year of age.[28,30] Furthermore, Healthy People 2020 objectives MICH-21 focuses on increasing the proportion of infants who are breastfed.[31]

Post birth, infant feeding is a key factor influencing infant growth. Infant growth is influenced by both the quantity and quality of infant feedings.[5,32–34] The relationship between infant feeding type and infant growth is apparent in distinct growth patterns of breastfed versus formula fed infants.[35] Since breastfeeding is considered the gold standard for infant nutrition, ideal growth targets are based on the average weight and length of breastfed infants.[36] Breastfeeding plays a protective role in the regulation of infant growth by inhibiting excessive growth during infancy.[37–40] In contrast, formula feeding may be associated with an elevated risk of excessive growth during infancy.[35,36] The suboptimal growth trajectory of formula fed infants may predispose these infants to poor child growth and health outcomes.

Study aims:

It is reasonable to consider both fetal and infant growth on a single growth continuum in which pre-pregnancy BMI and GWG during pregnancy and feeding behaviors during infancy are the driving forces influencing growth. Given the importance of GWG and infant feeding practices as determinants of infant growth, it would be informative to better understand their synergistic effect on infant growth.[30,22] A more nuanced understanding of the association between GWG, infant feeding, and infant growth could better highlight the pregnancy and early infancy periods as important points of intervention and inform the development of best practices in obstetrics and pediatrics.

I propose to examine the association between GWG, infant feeding type, and growth during infancy. More specifically, my aims are as follows:

- **Aim 1:** Determine at which point in time (i.e., three, five, seven, and twelve months of age) the association between gestational weight gain and three conditional growth outcomes (i.e. length, weight, and weight-for-length) is statistically significant.
- **Aim 2:** Determine at which point in time (i.e., three, five, seven, and twelve months of age) the association between feeding type and three conditional growth outcomes (i.e. length, weight, and weight-for-length) is statistically significant.
- **Aim 3:** Describe the change in the growth trajectory by feeding type.
- **Aim 4:** Examine if infant feeding moderates the association between GWG and infant growth.

Data and sample:

To perform these analyses, I will utilize the Infant Feeding Practices Study II (IFPS II) dataset; a large longitudinal cohort study on infant feeding in the United States.[41] Led by the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC), this study examined in detail breastfeeding perceptions, initiation, and duration.[41]

Chapter 2: Fetal Growth

Overview of fetal growth:

Fetal growth is the precursor for future growth and development. After conception, the egg and sperm form the zygote and travel down the fallopian tubes to the uterus.[8] The structure that forms during early cell differentiation is referred to as the blastocyst.[42] In days 5 and 6, the blastocyst reaches and implants on the inner wall of the uterus and the cells differentiate to form the embryo and placenta.[8] The cells of the embryo then multiply and begin to take on specific functions.[10]

A number of growth processes occur simultaneously in preparation for survival post-birth. As the first trimester continues, major organ systems such as the brain, spinal cord, heart, and lungs, begin to form and become interconnected and external structures such as the eyes and ears are in the early stages of development as well.[9] By five weeks gestation, arm and leg buds become visible, the brain develops into five distinct areas, the vertebra and other bone structures start to take form, the heart beats rhythmically, and blood begins to circulate.[43] By the sixth-to eighth weeks of gestation, all essential organs are developing, the limbs have grown substantially, hands and feet are distinguishable, and external features such as facial features take their final shape. The eighth week marks the end of the embryonic period and the start of the fetal period.[43]

By the second trimester, skeletal and muscle systems form to protect the developing internal organ systems.[10] During this period, the fetus has a distinct human appearance, gains the ability to see and hear, and the limbs continue to develop.[11] Between 9-12 weeks of gestation, the head has grown to be about half the size of the fetus, genitals appear, and the fetus can make a fist.[43] Shortly thereafter (i.e. 13-16 weeks gestation) the bones harden and the fetus becomes active in the womb. By 20 weeks gestation, lanugo covers the body, eyebrows and lashes appear, and nail growth is visible on the fingers and toes.[43] By the end of the second trimester, the intricate respiratory and nervous systems are becoming more established. During the third trimester, organs mature at a rapid pace to enable the fetus to survive outside the womb.[11] By week 40 of gestation, the lanugo disappears, bones are fully developed, body fat accumulates, and the baby begins to store essential nutrients. Table 1 summarizes the average length and weight during embryonic and fetal development.

Table 1: Average Length and Weight During Embryonic and Fetal Development

Gestational Period	Average Length	Average Weight
Embryonic Period		
1-4 weeks	3/16 in.	weight is too small to estimate
5-8 weeks	1.25 in.	1/30 oz.
Fetal Period		
9-12 weeks	3 in.	1 oz.
13-16 weeks	6.5-7 in.	4 oz.
17-20 weeks	10-12 in.	0.5-1 lbs.
21-25 weeks	11-14 in.	1.25-1.5 lbs.
26-29 weeks	13-17 in.	2.5-3 lbs.
30-34 weeks	16.5-18 in.	4.5-5 lbs.
35-38 weeks	20 in.	7-7.5 lbs.

[43]

Fetal growth is subject to a number of influences including but not limited to maternal factors; such as diet, metabolism, pre-pregnancy BMI, physiologic changes associated with pregnancy and GWG.[15] Although the fetus is remarkably resilient, the pregnancy period is a sensitive phase of development during which a suboptimal maternal-fetal environment can disrupt the fetal growth trajectory and negatively impact the health of the fetus.

Maternal influences on fetal growth:

Maternal pre-pregnancy BMI and GWG play an integral role in fetal growth and development as the fetus relies on the mother as the sole source of nutrition.[44] Pre-pregnancy BMI and GWG play an important role in fetal growth outcomes; however, I must acknowledge that these are merely select factors embedded within the larger biologic, environmental, and social contexts. Maternal diet during pregnancy plays a critical role in fetal growth. Low maternal nutrient intake is associated with an increased risk of small for gestational age (SGA) newborns and high nutrient intake with risk of macrosomia or large for gestational age (LGA) newborns.[45,46] Although low nutrient availability is generally associated with poor fetal growth; the association between nutrient availability and growth may also be dependent on the stage of pregnancy. During the Dutch famine (1944-1945), a relative reduction in total food intake in early pregnancy, followed by increased access to food in late pregnancy was associated with heavier birth weights compared to newborns born before or after the famine.[47] In addition, nutritional deprivation during late pregnancy was associated with lower birth weights.[47] Both the quality and timing of maternal nutrient intake has an influence on fetal growth. In addition to maternal diet, maternal metabolism also influences the rate at which the fetus receives essential nutrients. Maternal metabolic rate varies by hereditary factors and pre-pregnancy maternal nutritional status. Complex metabolic changes take place during pregnancy to ensure optimal fetal growth within the constraints of the maternal-fetal environment.[48]

The placenta, which is the intermediary between the mother and fetus, enables nutrients and oxygen to pass from the mother to the fetus and regulates fetal growth through the production of hormones. Throughout pregnancy there is a dynamic relationship between maternal factors (i.e. pre-pregnancy BMI, GWG, and maternal metabolism), placenta growth and function, nutrient availability, and uterine-artery blood flow. [44,22] On average, obese women are more likely to have a larger placenta and give birth to larger infants in comparison to women in the normal weight range.[22] Changes in maternal homeostasis can modify placental structure and function thereby impacting fetal growth.[22] During pregnancy, the placenta triggers hormonal changes which modifies maternal metabolic processes.[8] Maternal behaviors during pregnancy; such as physical activity, further influence metabolic processes which may positively affect the amount of nutrients available for fetal growth.[48]

The mother also undergoes physiologic changes to improve transport mechanisms to meet the needs of the gestating fetus.[44] During pregnancy, the total maternal blood volume and cardiac output increase by approximately 40%.[49] Uterine-artery blood flow may increase as much as three times during pregnancy as a result of increased artery diameter, reduced resistance to blood flow, and the appearance of new blood vessels in the uterus.[50] These adaptive physiologic processes result in increased capacity to deliver nutrients from the mother to the fetus.

Furthermore, evidence shows that the presence of growth-regulating hormones, such as insulin-like growth factors (IGFs) and leptin, in cord blood is positively associated with birth weight; indicating that fetal growth is at least in part dependent on growth regulating hormones.[44,51–53] Glucocorticoids also play a critical role in fetal organ development.[44,54] Maintaining adequate levels of IGFs, leptin, and glucocorticoids are essential to a positive birth outcome.

Birth outcomes such as birth weight and size, generally reflect the intrauterine experience. Birth weight and size in part mirror maternal nutrition, behaviors, and GWG during pregnancy.[25] At birth, a newborn's growth is classified into one of three categories: appropriate for gestational age (AGA) defined as the 10th-90th percentiles for gestational age, LGA which is greater than the 90th percentile, and SGA defined as less than 10th percentile category.[55] An improved understanding of the association between pre-pregnancy BMI/GWG and birth weight/size has contributed to modifications to the guidelines for weight gain during pregnancy.[22]

Pre-pregnancy BMI and GWG

History:

The recommendations for weight gain during pregnancy have changed dramatically over the years reflecting an improved understanding of the maternal-fetal relationship. In the 1920's, efforts were made to restrict maternal weight gain in an attempt to facilitate labor and the woman's ability to return to their pre-pregnancy weight.[56] By the 1940s, women were advised to avoid excessive weight gain; as it was believed that excessive weight gain was associated with preeclampsia.[57] In the 1960s, guidance to restrict weight gain during pregnancy resulted in babies born SGA, LBW, and with serious life threatening conditions that continued beyond the neonatal period. These concerns about LBW led to studies focused on the relationship between GWG and birth weight.[58–60] The National Academy of Sciences then published the *Maternal Nutrition and the Course of Pregnancy* in 1970, where women were encouraged to eat according to their individual appetites and to gain a minimum of 24 pounds.[61] The 1990 IOM report[15] recognized pre-pregnancy BMI as an important consideration when developing recommendations on GWG and the report made specific weight recommendations for subgroups, such as adolescents, groups defined by race/ethnicity, women of short stature, and women carrying twins.[22]

Since the release of the 1990 IOM report, the U.S. population has experienced a change in demographic characteristics including a more diverse childbearing age and an increase in pre-pregnancy BMI and GWG across all population subgroups. The National Health and Nutrition Examination Survey (NHANES) 2003-2004 data show that 28.9% of women of childbearing age (20-39 years old) were obese (BMI $\geq$ 30 kg/m2) and 8% were extremely obese (BMI $\geq$ 40 kg/m2).[62] In addition, women are entering pregnancy at an older age and increasingly must manage co-morbid conditions; which increase the risk for pregnancy complications.[22] These factors contributed to the need to revise the IOM report on pregnancy nutrition in 2009.[22]

Current state of science:

The current recommendations on GWG were derived from three data sources: birth certificates, CDC's Pregnancy Risk Assessment Monitoring System (PRAMS), and CDC's Pregnancy Nutrition Surveillance System (PNSS).[22] An IOM Committee charged with revisiting the GWG recommendations concluded that less than half of pregnant women have met the recommendations set-forth in the 1990 IOM guidelines for GWG.[22] The IOM committee additionally concluded that specific recommendations for women of short stature, by ethnicity/race, and adolescents, women categorized as obesity classes II and III, and smokers were unwarranted. There was insufficient evidence to support modified recommendations for these subgroups. It was determined that only multiparous women should follow alternate GWG guidelines.[22]

The revised IOM report includes ranges of optimal weight gain based on pre-pregnancy BMI (Table 2).[22] In addition, the pre-pregnancy BMI cut-offs used in the 2009 report differ from those used in the 1990 report. The 2009 report adopted the WHO guidelines for pre-pregnancy BMI cut-offs among non-pregnant adults for use in categorizing pre-pregnancy BMI. This change reduces the proportion of women in the underweight and obese groups and increases the proportion of women in the normal and overweight ranges.[22] In addition, the new guidelines include a relatively narrow range of recommended weight gain for obese women.[22]

A universal recommendation for weight gain during pregnancy cannot be issued since the effect of maternal weight gain on birth weight varies by pre-pregnancy BMI and maternal anthropometric measures.[63] As previously mentioned, the recent weight gain recommendations are based on a woman's pre-pregnancy BMI. The IOM guidelines recommend that women with a BMI < 18.5 kg/m^2 should gain 28-40 lbs.; those with a BMI of 18.5-24.9 kg/m^2 should gain 25-35 lbs.; those with a BMI of 25-29.9 kg/m^2 should gain 15-25 lbs.; and those with a BMI > 30.0 kg/m^2 should gain 11-20 lbs. (Table 2).[22] Furthermore, the revised recommendations take into account both maternal and fetal health outcomes.[64] In addition, the rate of GWG varies by trimester. Weight typically increases slowly in the first trimester; however, the second and third trimesters experience greater increases to support rapid fetal growth.[65]

Table 2: Institute of Medicine Recommendations for Weight Gain during Pregnancy

Pre-Pregnancy BMI	BMI (kg/m^2)	Total Weight Gain (lbs)	Rates of Weight Gain* 2nd and 3rd Trimester (lbs/week)
Underweight	<18.5	28-40	1 (1-1.3)
Normal weight	18.5-24.9	25-35	1 (0.8-1)
Overweight	25.0-29.9	15-25	0.6 (0.5-0.7)
Obese (includes all classes)	≥30	11-20	0.5 (0.4-0.6)

*Calculations assume a 0.5-2 kg (1.1-4.4 lbs) weight gain in the first trimester.[22]

Current controversies:

It is well established that underweight women who do not gain enough weight during pregnancy are at risk for SGA and preterm birth.[66, 67] Data on mothers with inadequate GWG have unequivocally supported the benefits of increasing total weight gain recommendations for underweight women in reducing the risk of SGA and preterm birth.[66,67] Recommendations for obese pregnant women have been more controversial since greater weight gains in obese pregnant women increases the risk of pre-eclampsia, LGA, cesareans, and birth complications.[22] Optimal GWG recommendations continue to be debated as pre-pregnancy maternal obesity has increased significantly over the past 15 years with average maternal body weight at the first prenatal visit increasing by 20%.[68,69] Pre-pregnancy maternal obesity is a recognized predictor of pregnancy complications and infant health risk.[70]

Many health professionals and researchers advocate lowering IOM's weight gain recommendations for obese pregnant women. Current birth weight trends mirror maternal obesity trends with an increasing number of infant birth weights greater than the 90^{th} percentile and greater than 9 lbs.[71] This is cause for concern as birth weight can be viewed as a reflection of the intrauterine experience, which sets the stage for childhood growth trajectories. Discussions are underway to assess the recommendations for weight gain among obese pregnant women.[72,73] It has been proposed that the weight gain recommendations for this subgroup should be differentiated further by classes of obesity.[74,67] Some suggest that women classified as extremely obese should lose weight during pregnancy.[64] Pre-pregnancy BMI and GWG are undoubtedly critical to fetal growth and development.

Pre-pregnancy BMI and birth weight literature review:

A number of studies have examined the association between maternal pre-pregnancy BMI and birth weight.[63,70, 75–77] In a multi-site hospital-based study (N=712), women with a BMI ≤ 20 gave birth to infants with a higher prevalence of LBW (39.5%) compared to women with a BMI between 20-25 (24.2%), overweight (16.4%), and obese (14.9%).[63] A cohort of mother-infant dyads (N=130,549) also reported a positive association between maternal pre-pregnancy BMI and infant birth weight ($p<0.01$).[76] Among a sample of mother infant dyads (N=395) maternal pre-pregnancy BMI, predicted birth weight ($r=0.30$).[77] Among a community-based sample (N=72), infants born to mothers with a normal pre-pregnancy BMI have significantly lower percent fat (12.5% +/- 4.2% vs. 13.6% +/- 4.3%; $p<0.01$) less fat mass (414.1 g+/- 264.2 g vs. 448.3 g +/- 262.2 g; $p<0.05$) and more fat-free mass (3310.5 g +/- 344.6 g vs. 3162.2 g+/- 343.4 g; $p<0.05$) than infants born to overweight or obese mothers.[75] These studies indicate that pre-pregnancy BMI is positively associated with fetal growth outcomes; however, GWG may also have an influence on fetal growth outcomes.

GWG and birth outcomes literature review:

Studies have consistently demonstrated an association between GWG and birth weight.[78,79,80] A population-based cohort of women (N=513,501) and their offspring (N=1,164,750) found an association between GWG and birth weight (19.98 OR, 95% CI 7.10–7.59, p<0.01).[79] Infants of mothers who gained 20-22 kg weighed about 104g (97.0–110.6) more compared to the reference group of women who gained 8–10 kg, and infants of mothers who gained greater than 24 kg weighed about 150g (141.7–156.0) more than the reference group.[79] Essentially, the greater the GWG, the heavier the baby at birth. Within a cohort of 3,015 mother-infant dyads, each kg of total GWG was associated with a significant increase in birth weight percentile of 1.60 (95% CI=1.39, 1.82), a significant decrease in odds of SGA of 0.89 (95% CI=0.86, 0.91) and a significant increase in odds of LGA of 1.13 (95%CI=1.10, 1.17).[78] A retrospective cohort using CDC's PRAMS data (N=104,980) found that women who gained 1-4 lbs. during pregnancy had as much as a 1.5 greater odds (95% CI, 1.2-1.8) of SGA compared to women who gained 15-25 lbs. during pregnancy.[80]

Furthermore, a systematic review of 25 studies, conducted by the Agency for Healthcare Research and Quality (AHRQ), of GWG and birth outcomes (1990-2007) evinced an association between GWG and a number of birth outcomes including: total birth weight, LBW, preterm birth, SGA, and LGA infants. All 25 studies reported a positive association between GWG and birth weight. On average, infants born to women in a high GWG category weighed 300g more than infants born to women in a low GWG category. This review concluded that for every 1kg increase in GWG, birth weight increased 16.7-22.6g.[81] Some studies included in the AHRQ review examined the relationship between GWG and LBW (i.e., birth weight < 2,500 g).[81] These studies demonstrated that the risk of LBW decreases as GWG increases. Other studies focused on the risk of macrosomia (i.e., birth weight >4,500g). These studies showed the relative risk for macrosomia was 2-3 times higher among women in the highest GWG category compared to infants born to women in the lowest GWG category.[81] These data indicate that a positive association between GWG and birth weight is apparent across the full range of maternal weights.

Pre-pregnancy BMI and GWG on size at birth/birth weight:

Both pre-pregnancy BMI and GWG independently influence infant birth outcomes. The following literature review demonstrates the importance of considering GWG in the context of pre-pregnancy BMI. In a prospective cohort of mother infant dyads (N=3,000), both pre-pregnancy BMI ($\beta = 44.7$, P = 0. 01) and GWG ($\beta = 19.5$, $p < 0.01$) were positively associated with birth weight.[18] Furthermore, the risk of LGA increased with increasing pre-pregnancy BMI and GWG ($p < 0.01$).[18] Among a hospital-based sample of 2,946 live births, the association between GWG and birth weight was significant in all maternal weight categories with the exception of mothers categorized as very overweight, defined as gaining greater than approximately 44 pounds over the course of the pregnancy.[82] For every one-unit increase of pre-pregnancy BMI, there was a 15.9g increase in birth weight after controlling for confounders and GWG. The association between GWG and birth weight was significant for the underweight, ideal weight, and moderately overweight women. This study also reported that GWG had a greater impact on birth weight among underweight women.[82] Interestingly, this study found that birth weight was not influenced by GWG among the very overweight women. This is consistent with the most recent IOM Report, which suggests that higher pre-pregnancy BMI may reduce the impact of GWG on birth weight.[22]

A population-based study in Denmark (N=60,892) found a positive association between pre-pregnancy BMI/GWG and the risk of infants born LGA. In addition, underweight women (BMI< 18.5 kg/m^2) with low GWG (<10 kg) increased the risk of the infant being born SGA compared to women with a normal pre-pregnancy BMI (18.5-25 kg/m^2) and GWG between (10-15 kg). Furthermore, women who were underweight with high GWG (16-19 kg) could have potential benefit to infant birth weight. Including both pre-pregnancy BMI and GWG in the model as an interaction term resulted in an increased odds of infants born SGA/LGA by 5.5 compared to the odds ratio in the basic model in which the independent risk factors of pre-pregnancy BMI and GWG were 3.4 (1.8 x 1.9).[19] In another population-based sample of mother-infant dyads (N=245,256), obese women with low GWG had a 0.66 decreased risk of infants born LGA (95% CI: 0.59-0.75).[17] In addition, there was approximately a three-fold increased risk of infants born LGA among women with a normal pre-pregnancy BMI and high GWG as well as women who were classified as underweight pre-pregnancy BMI and high GWG.[19,17] In accordance with the IOM recommendations, studies should consider GWG in the context of-pregnancy BMI to improve the utility of the analyses.[22] Since the IOM recommendations only became available in 2009, studies using this standard are limited. The IOM recommendations can provide the framework for future analyses. Introducing a new set of parameters can lend itself to a shift in research findings resulting in a change in the magnitude of the association between pre-pregnancy BMI/GWG and birth outcomes.

Studies focusing on pre-pregnancy BMI/GWG and size at birth/birth weight relate to infant growth and later childhood BMI since growth can be viewed on a continuum from conception through adolescence.[83] Infant size at birth and birth weight sets the stage for the next successive phase of growth during infancy, yet none of the studies reviewed assess the association of pre-pregnancy BMI/GWG beyond birth outcomes. Early indicators of growth can provide valuable information on an individual's future growth trajectory. Additional research is needed to better understand the influence of maternal factors on fetal and infant growth.

Chapter 3: Infant Growth

Infant growth is a reflection of a complex web of hereditary and environmental factors; among which, infant feeding is one of the most important determinants. Below, I will highlight the importance of the rate of growth, growth trajectories, and feeding type, and review the current literature on infant feeding and growth.

Growth rate:

Growth involves both developmental and adaptive processes in length and weight over time. The rate of growth during infancy is more rapid than in any other life stage.[84] During infancy, length typically increases by 50% and weight triples.[85] However, infant growth is not a linear process. Newborns can lose up to 10% of their birth weight in the first 2-3 days of life and regain their birth weight by 10-14 days of life.[55] Growth continues in spurts as well as periods of slower growth. A focus on growth during infancy is of public health significance since growth during this time is fundamental for future growth and development.

Growth trajectories and patterns:

Birth weight, catch-up and slow-down growth during infancy:

Infant growth can be viewed as the continuation of fetal growth; since infant growth often compensates for growth restraints or growth enhancements experienced in utero. During infancy, a LBW or SGA infant must gain weight at a faster rate (i.e., catch-up growth) compared to an infant born at a normal weight. Catch-up growth is generally viewed to be desirable, since it signifies a normalization of growth in comparison to earlier suboptimal growth.[86] However, there is some evidence that SGA or LBW infants who experience catch-up growth are at greater risk for developing poor health outcomes during adulthood, such as type 2 diabetes and metabolic syndrome.[87,88] In contrast, high birth weight or LGA infants may experience slow-down growth.[89] This is viewed as a natural, desirable adaptation. However, parenthetically, it is worth noting that caregivers may counteract the weight loss that accompanies slow-down growth by overfeeding infants.[90] This overconsumption increases the risk of childhood overweight/obesity, cardiovascular disease, and diabetes.[90]

Feeding type and growth:

In addition to physiologic adaptive processes, growth trajectories also reflect infant feeding practices, as evidenced by distinct growth patterns of breastfed and formula fed infants. [e.g., 32, 35, 91–93] In general, breastfed infants experience a slowing of growth during infancy compared with formula fed infants; however, the timing of these differences in growth is variable across studies. The estimated magnitude of the association between breastfeeding, formula feeding, and growth appears to be influenced by methodological issues, inconsistent definitions of feeding type, and the observed duration of infant feeding.[94]

Classification of infant feeding: type, quantity and duration:

The classification of infant feeding depends on the study aims and other practical considerations. In the absence of clinical assessment of dietary intake, epidemiologic studies often rely on maternal recall of feeding type, quantity, and duration of infant feeding.[95–97] Investigators often categorize infants into exclusive feeding categories; however, since the precise amount of breast milk or formula consumed is not always readily available and exclusivity is rarely maintained through the first six months of infancy, degree of exclusivity is widely accepted as a measure of infant feeding.[96] Some researchers estimate the proportion of breast milk over total feeds as a proxy for quantity. Other researchers select an empirically determined cut-off point to maximize variation and increase the statistical power within each study. Although both exclusive and predominant/proportional infant feeding definitions are commonplace in the literature, the definitions of these terms vary by study. The following studies reflect this variability in definitions and highlight the need for the harmonization of terminology.

Infant feeding and growth literature review:

Exclusive feeding:

The following studies incorporate measures of *exclusive* feeding to examine infant growth. Among a cohort of infants from the Republic of Belarus (N=17,046), the greatest difference in weight and length between breastfed and formula fed infants was observed between three and six months of age.[92] Compared to exclusively breastfed infants, both partially breastfed infants and formula-fed infants experienced a higher weight-for-age Z-score [partially breastfed: +0.125 (95% CI: +0.096 to +0.154); formula fed: +0.139 (95% CI: +0.116 to +0.162)] and a higher length-for-age Z-score [(partially breastfed: +0.081 (95% CI: +0.046 to +0.116; formula fed: +0.075 (95% CI: +0.047 to +0.102)].[92] Among a cross-sectional representative sample of U.S. infants, (N=5594) infants exclusively breastfed for four months weighed approximately 0.2 kg less and had a 0.27 lower weight-for-length Z-score at 8-11 months compared to infants fed formula and other foods ($p<0.05$).[93]

Proportion of feeds:

The following studies examine the proportion of feeds. In a meta-analysis of 19 studies comparing the weight of breastfed and formula fed infants of varying proportions, formula fed infants gained 600-650g more than breastfed infants during infancy.[32] This difference was apparent in the first four months post birth but most pronounced between six and twelve months of age.[32] In the majority of the studies reviewed, infant length was similar between the two feeding groups.[32] Among a cohort of infants in Davis, CA (N=867), predominant breastfed and formula fed infants had similar weight gain in the first three months; however, predominantly breastfed infants gained 0.65 kg less than formula fed infants by twelve months of age ($p < 0.05$); infant length measures were not significantly different.[35]

Some of the studies that have adopted proportional or predominant feeding definitions have focused on the association between infant feeding and later childhood obesity. As this is not the focus of my analysis, the description of study design and findings have been omitted but the classification of infant feeding variables is relevant and can inform studies on infant feeding and growth. Classification categories may adopt both exclusive and predominant infant feeding categories; for example: breast milk only, more breast milk than formula (i.e., >50% breast milk), both equally, more formula than breast milk (i.e., >50% formula), or formula only, and incorporate a measure of the duration of breastfeeding.[98] Other studies adopt vague definitions such as partly breastfed for greater than or equal to three months compared to partly breastfed for up to three months combined with those bottlefed.[99] Other studies combine exclusive and proportional breastfeeding categories; for example: never breastfed compared to partly and exclusively breastfed for more than six months.[100]

As evidenced by the literature, there is variability in parameterization of infant feeding. This variability can impact the estimate of the true underlying association between infant feeding and infant growth. This inconsistency can make it difficult to compare findings across studies. In sum, the majority of the aforementioned studies reported slower weight gains among breastfed infants compared to formula fed infants, despite differences in the timing of when a weight difference was noted. The relationship between infant feeding type and length was inconsistent among the studies reviewed.

Growth charts:

Monitoring and assessing infant growth is important for both short-term and long-term health outcomes.[36] Both the CDC[36] and the WHO[14] have constructed growth charts to allow comparisons of an infant's growth against a reference population. The CDC growth charts reflect growth of U.S. children based on data collected from five cross-sectional nationally representative surveys administered between 1963 and 1994.[101] Rather than ideal growth patterns, the CDC standards represent typical growth patterns of U.S. born infants and should not be used as the standard for early growth because of the high prevalence of obesity among U.S. children.[36] The WHO growth charts were derived from longitudinal data from six countries from 1997-2003 and were based on the optimal growth of infants predominantly breast-fed for at least four months and who continue to breastfeed at least partially through 12 months of age.[36,102] Since The CDC growth charts reflect population norms and the WHO growth charts represent ideal growth targets, the CDC recommends use of the WHO growth curves for assessing growth of infants from birth through two years of age.[36] Both the CDC and WHO growth charts display weight-for-age, length-for-age, and weight-for-length Z-scores.[103]

Study aims:

The aims of my study are as follows:

- **Aim 1:** Determine at which point in time (i.e., three, five, seven, and twelve months of age) the association between GWG and three conditional growth outcomes (i.e. length, weight, and weight-for-length) is statistically significant.
- **Aim 2:** Determine at which point in time (i.e., three, five, seven, and twelve months of age) the association between feeding type and three conditional growth outcomes (i.e. length, weight, and weight-for-length) is statistically significant.
- **Aim 3:** Describe the change in the growth trajectory by feeding type.
- **Aim 4:** Examine if infant feeding moderates the association between GWG and infant growth.

Chapter 4: Methods

Research design and methods:

The Infant Feeding Practices Study II (IFPS II), administered by the FDA and CDC, is a large, longitudinal U.S. study of infant feeding and care practices during infancy.[41] The study sample was drawn from a national database of households who volunteered to complete a series of surveys on a variety of topics.[41] Women in their third trimester of pregnancy who were at least 18 years old at the time of the initial survey were eligible for participation in the study.[41] To continue participation post birth, the infants had to be at least 35 weeks gestation, weigh at least 5 pounds, be a singleton, the mother and baby had to be healthy at birth, and the infant had to be free of any condition likely to affect feeding.[41,104] Subsequent to enrollment, infants were excluded if they developed a medical condition that would affect feeding but their data up to that point were included in the analytic files. In addition, participants who lived in a zip code impacted by the 2005 Gulf Coast hurricanes were excluded due to disruptions in mail delivery services.[41] The IFPS II surveys were administered as follows:

Table 3: IFPS II Sample Size and Response Rates

	Prenatal	Birth Screener	Neonatal	Month								
				2	3	4	5	6	7	9	10	12
Sample Size (N)	4902	3452	3033	2552	2388	2238	2183	2095	2020	1944	1808	1807
Response Rate (%)*	N/A	82.9	76.9	83.1	78.9	74.7	73.1	70.9	68.9	67.0	63.3	64.5

*Response rate: (No. of surveys completed/adjusted No. mailed - No. of women disqualified)

A total of 15,147 women in their third trimester of pregnancy were mailed an initial questionnaire inquiring about infant feeding choices, medical history, and the mother's social support system. A total of 4,902 were deemed eligible for participation in the study. Among the 4,902 who completed a prenatal survey, 3,452 respondents completed a birth screener (either by telephone, automated voice response, or mailing at or around the women's expected due date), 3,033 respondents successfully completed the neonatal survey (by mail) at approximately three weeks postpartum, and 1,807 women successfully completed nine postpartum surveys (by mail) approximately monthly through seven months of age and approximately every seven weeks until the infant was twelve months of age.[41] Participants were required to complete the prenatal and neonatal surveys to receive the postpartum surveys. The surveys were administered from May 2005 through June 2007. Participants received a gift valuing less than $3 for completing each questionnaire.[41,104] The strengths and limitations of the IFPS II are described in the discussion.

Key variables:

The following variables were included in the analysis:

Pre-pregnancy BMI (prenatal survey): *"What was your weight just before you became pregnant? ________ pounds"* Responses were converted from pounds to kilograms and categorized according to the IOM pre-pregnancy BMI categories: underweight (< 18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese (> 30.0 kg/m^2).[22]

Gestational weight gain (GWG) (neonatal survey): *"How much weight did you gain* *during this pregnancy? ________ pounds"* A pre-pregnancy BMI categorical variable was created to classify the continuous GWG responses as under, within, or over the IOM recommended ranges: women who are underweight gain 28-40 pounds; normal weight gain 25-35 pounds; overweight gain 15-25 pounds; and obese gain 11-20 pounds.[22] Each woman was then classified as gaining inadequate, adequate, or excessive GWG.

Infant feeding (neonatal, months two and three)**:** *"In the past 7 days, how often was your baby fed each food listed below? Include feedings by everyone who feeds the baby and include snacks and night-time feedings."* The responses ranged from nine items on the neonatal survey to 19 items on the month three survey; reflecting typical foods that may be introduced at later ages (See Appendix A.1).

Both the WHO and the American Academy of Pediatrics (AAP) recommend exclusive breastfeeding until six months of age and the introduction of solid foods at six months.[105,106] However, most families do not adhere to this recommendation. In this dataset only 4% of the sample was exclusively breastfed at six months. Since this is insufficient, predominant feeding categories were defined to assess the influence of the infants' predominant source of nutrition on infant growth.[e.g. 98,107] The WHO definition for predominant feeding can be interpreted as ≥ 51%-99%.[29] Ideally, the cutoff for predominant feeding should be as close to 100% as possible.

The choice of a cut-off for predominantly feeding categories was empirically driven. The criterion for this decision was to have approximately 30% of the sample represented in the predominant breastfed and formula fed categories. Based on this criterion, I defined three infant feeding categories using 70% as the predominant feeding cut-off:

1) predominantly breast milk feeds, ≥ 70% of daily feeds is breast milk,

2) predominantly formula feeds, ≥ 70% of daily feeds is formula,

3) mixed feedings, defined as all other combinations of feedings.

The feeding categories were calculated by taking the proportion of breast milk feeds over the sum of total feeds multiplied by 100, the proportion of formula feeds over the sum of total feeds multiplied by 100, and the proportion of mixed feeds over the sum of total feeds multiplied by 100. The proportion of feeds data was used as a proxy for dietary intake.

Infant weight (months three, five, seven, twelve): *"How much did your baby weigh the last time he or she was weighed at a doctor's visit ________ POUNDS ________ OUNCES Don't know ________?"* Infant weight was estimated from continuous repeated measures.

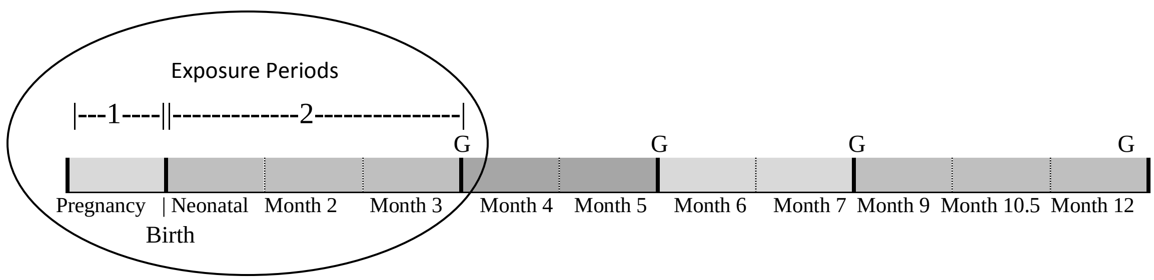
Infant length (months three, five, seven, twelve): *"How long was your baby the last time he or she was measured at a doctor's visit* ________ INCHES Don't know ________?" Infant length was estimated in inches from continuous repeated measures.

Infant weight-for-length (months three, five, seven, twelve): Infant weight-for-length was computed by dividing weight by length for each time point.

Exposure periods:

The exposure window for this analysis spans from pregnancy through month three. Pre-pregnancy BMI and GWG data were collected during pregnancy (exposure period 1) and infant feeding data were collected from birth through month three (exposure period 2) (see Figure 1). Although the AAP recommends exclusive breastfeeding through six months of age, exclusivity is rarely maintained and infants are typically introduced solid foods between five and six months of age.[28,30,108] Restricting the infant feeding exposure period from birth through month three minimizes diet variability as most infants will be predominantly breastfed or formula fed and this exposure period aligns with the available growth data.[109] In other words, the exposure window proceeds the assessment of growth outcomes. The infant feeding responses were analyzed by aggregating the available feeding data from birth through month three by taking the sum of reported breast milk feeds on the neonatal, month two, and month three surveys and dividing by the total number of feeds reported on these surveys. The average predominantly formula fed and average mixed fed was determined using the same approach.

Figure 1: Schematic displaying distinct exposure periods from pregnancy through three months of age



G=Growth data available (i.e. outcome variables)

Outcomes:

Weight, length, and weight-for-length were calculated at months three, five, seven, and twelve. The benefit of weight and length is that they are based on real values as opposed to a proportion. Whereas, weight-for-length is used to determine proportionality and is not an absolute value. Weight-for-length is the only growth indicator that incorporates both weight and length as a composite measure. Age is inherently incorporated since weight-for-length data are analyzed at a specific age (e.g. month three survey). There may be some extreme cases where the proportion is the same even though the weight and length measures are very different. There was benefit to incorporating all three growth indicators within my analysis since it was unknown whether there would be an association with weight, length, or both.

Confounders:

The following variables were included in the models as potential confounders:

Race/ethnicity (demographic survey) [34,110,111,112]: "*Race: White, Black, Asian/Pacific Islander, Other*"

Maternal age (demographic survey): [34,110–113] *"Date of Birth ____/ 1 9 __ __ "*

Month / 4-digit year

Maternal age was recoded into four discrete categories: 18-21 years old, 22-31 years old, 32-41 years old, 42-52 years old.

Family income (demographic survey): [34,110,111] *"Please "X" the box which best describes the total yearly income of all members of your household before taxes. Please include any income from all sources-employment, pensions, social security, etc."*

The list of income categories that appeared on the questionnaires can be viewed in Appendix A.2. The income options were collapsed into the following categories: less than or equal to $19,999; $20,000-$39,999; $40,000-$59,999; $60,000-$99,999; and greater than or equal to $100,000.

Prenatal smoking: (prenatal)- [113,111]: **"***On the average, how many cigarettes do you*

*smoke a day now? (Write in 0 if you do not smoke)*_________*CIGARETTES PER DAY*.
Responses were recoded into the following categories: no cigarettes, 1-10 cigarettes per day, and 11-20 cigarettes per day.

Sex of infant- (neonatal survey)-*"Is your baby a boy or a girl?* ________ *Boy* ________ *Girl."* Infant growth targets are sex specific and therefore the sex of the infant was incorporated within the analysis.[14]

Introduction of solid foods (neonatal, months two and three):[110,113] The responses to the food frequency questionnaire on each survey were reviewed to determine when the infant was introduced solid foods (see Appendix A.1 for the neonatal questionnaire excerpt). Each survey included a different list of solid foods. The introduction of solid foods was included in the model as an indicator variable to control for the introduction of solid foods during exposure period 2 (i.e., birth to month three).

Birth weight (birth screener):[34,110,113] *"How much did your baby weigh at birth*

POUNDS _____AND OUNCES______" Birth weight was included in the model assessing postnatal weight outcomes to assess conditional weight gain or postnatal weight gain controlling for the infants' weight at birth.

Birth length (neonatal survey):[34] *"What was your baby's length at birth?* ________ INCHES"

Birth length was included in the model assessing postnatal length outcomes to assess conditional length gain or postnatal length gain controlling for the infants' length at birth.

Weight-for-length at birth (neonatal survey): The ratio of weight-for-length at birth was included in the model assessing postnatal weight-for-length outcomes to assess conditional weight-for-length gain or postnatal weight-for-length gain controlling for the infants' weight-for-length at birth.

The following confounders were excluded from the analysis as a result of multicollinearity or in an effort to obtain a parsimonious model. In addition, where multicollinearity was present the variables with the most missing and the least variability were excluded:

Marital status (demographic survey):[34,112] *"What is the marital status of the female and/or male head of household? Now married, Widowed, Divorced, Separated, Never Married"*

Maternal education (demographic survey): [34,110–113] *"Please indicate the HIGHEST level of education completed by the female and male head of household:*

___1-7 years grade school

___8 years grade school

___1-3 years high school

___High school graduate

___1-3 years college

___College graduate

___Post graduate"

A response of 1-7 years grade school, 8 years grade school, or 1-3 years of high school were combined into a single category. Only information about the maternal education was included in the analysis.

Prenatal care utilization (prenatal survey):[111,112] *"Who provides your prenatal care? An obstetrician; a family doctor, general practitioner, internist, or other physician; a midwife or nurse midwife; another type of health care provider."* This was modeled with a variable indicating whether or not the respondent received prenatal care (one) did not receive prenatal care (zero).

Maternal smoking: (month 3):[110,112] "*On the average, how many cigarettes do you smoke a day now? (Write in 0 if you do not smoke)*____________ *CIGARETTES PER DAY*. Responses were recoded into the following categories: no cigarettes, 1-10 cigarettes per day, 11-20 cigarettes per day, and more than 20 cigarettes per day.

Health insurance (prenatal survey):[112] "*Are you covered by any kind of health insurance or any kind of health care plan, such as insurance obtained through an employer or a government program like Medicaid? __Yes __No"*

Maternal height (prenatal survey):[113] *"How tall are you?* ____________ *FEET* __________ *INCHES."* Responses were recoded to create a categorical variable for mother's height: less than five feet, greater than or equal to five feet and less than five feet six inches, greater than or equal to five feet six inches and less than six feet, greater than or equal to six feet and less than seven feet, or greater than or equal to seven feet.

Parity (prenatal): [34,110,113,112] "*How many other babies have you had or adopted when younger than 12 months old? Do not include the baby you are expecting.*

_______ *OTHER BABIES HAD* ________ *BABIES ADOPTED.*

For the purpose of this analysis, only the responses in the "other babies had" response field were included. The parity data were recoded into the following categories: zero babies, one baby, two babies, three babies, or greater than or equal to four babies.

Analysis:

Bivariate associations of feeding type and growth during infancy were stratified by GWG category. For these bivariate analyses, the *p*-values for both normally distributed and skewed continuous outcomes were estimated with Kruskal Wallis one-way ANOVA and the median and lower quartile (Q1) and upper quartile (Q3) were reported. In addition, these data were used to calculate the percentage of infant growth gain for each feeding type stratified by GWG group.

A series of regression models were fit to determine at which point in time the association between GWG and infant growth (aim 1) and infant feeding and infant growth (aim 2) became significant. Aims 1 and 2 were achieved by analyzing the data as a panel study or cross-sections at each time point.

To determine how well the models fit the data, the fit of the full model (as assessed by -2Log likelihood statistic) was compared with that of reduced models with a chi square test with degrees of freedom equal to the difference in the number of parameters between the full and nested reduced models. For aims 1 and 2, separate models were fit for each of the following growth outcomes, denoted as E(Y): weight, length, and weight-for-length at months three, five, seven, and twelve.

It is important to note that in the models that included infant feeding as the independent variable: birth weight was included as a confounder when predicting weight, birth length was included as a confounder when predicting length, and weight-for-length at birth was included as a confounder when predicting weight-for-length. Only one birth outcome was included in a single model. Controlling for the growth measure at birth enabled an assessment of conditional growth or gain in growth measure. Growth measures at birth and infant feeding variables were excluded from the models where GWG was the independent variable since these growth measures are both on the causal pathway between GWG and postnatal growth and therefore were not considered potential confounders.

The models for Aim 1 (i.e. GWG and infant growth) were fit as follows:

E(Y) =βo +β1 (GWG)i + β2 (Race)i + β3 (Sex)i + β4 (Maternal Age)i + β5 (Prenatal Smoking)i + β6 (Income)i + β7 (Introduction to Solid Foods)i

The models for Aim 2 (i.e. infant feeding and infant growth) were fit as follows:

E(Y) =βo +β1 (GWG)i + β2 (Race)i + β3 (Sex)i + β4 (Maternal Age)i + β5 (Prenatal Smoking)i + β6 (Income)i + β7 (Introduction to Solid Foods)i + β8 (Growth Measure at Birth)i (i.e. birth weight, birth length, weight-for-length at birth) + β9 (Infant Feeding)i.

Mixed effect models were fit to describe the change in growth trajectory by feeding type (aim 3) and to examine if infant feeding moderates the association between GWG and infant growth (aim 4). Aims 3 and 4 required a longitudinal analysis in which the outcomes were assessed repeatedly over time and individual observations were likely to be correlated. In addition, the value of some of the covariates, such as infant feeding behaviors, change over time and lead to heterogeneity of variance over time. Mixed effects models accommodate both the correlation among repeated measurements and the heterogeneity of variance over time.[114] The random effects covariance structure allows the variance and covariance to change as a function of the time of measurement and also allows for between-subject and within-subject variability.[114,115] Of note, this approach does not require the same number of observations on each of the subjects in the analytic sample.[114,115] Mixed effect models are more forgiving in that they are able to accommodate these imbalances in the data.[115] A maximum likelihood estimation for incomplete data provides valid estimates and standard errors.[116,117]

To estimate the rate of change (i.e., slope) in infant growth by feeding type, a change point was identified; or a specific time point in which the slope for previous growth was compared with the slope for subsequent growth (denoted as t* in Equations 1 and 2 below). Month five was designated as a change point. This change point was used to compare the slope from month three to five versus the slope from month five to twelve. The following two equations were used to calculate the slopes.

Equation for estimating the slope before t*:

$E(Yij) = \beta o + \beta 1tij + \beta 3Xij + \beta 4Xijtij + \beta 5Xij\ (tij-t^*)^+ + bi$ (Equation 1)

Equation for estimating the slope after t*:

$E(Yij) = \beta o + \beta 1tij + \beta 2(tij-t^*)^+ + \beta 3Xij + \beta 4Xijtij + \beta 5Xij\ (tij-t^*) + bi$ (Equation 2)

E(Yij) = growth measures for the i^{th} subject at the j^{th} examination

βo=intercept

tij= is the observation time for subject i at the j^{th} examination

t*= change point

tij-t*= time minus change point

Xij =infant feeding type for the i^{th} subject at the j^{th} examination

Xijtij =the interaction of infant feeding and time

Xij (tij-t*) =the interaction of infant feeding and a change point

bi=random effect for the i^{th} subject

Note: In equation 1, where tij represents a time point before t*, $(tij - t^*)^+ = 0$. In equation 2, where tij represents a time point after t, $(tij - t^*)^+ = tij - t^*$. From equation 1, we can determine that the slope before t* is β1 + β4Xij. From equation 2, we can determine that the slope after t* is β1 + β2 + β4Xij + β5Xij. A detailed description of the calculations appears in Appendix B.

Finally, the difference in slopes between equations 1 and 2 is as follows:

(Slope before t*) β1 + β4Xij

(Slope after t*) - <u>β1 + β2 + β4Xij + β5Xij</u>

= - (β2 + β5Xij)

The difference in slopes - (β2 + β5Xij) is a function of infant feeding (Xij). The growth trajectories were assessed by fitting two interaction terms in one model, (1) the interaction of infant feeding variable with time as a continuous variable and (2) the interaction of infant feeding variable with $(tij-t^*)^+$. The models were fit separately for weight, length, and weight-for-length.

The final model for Aim 3 (i.e. growth trajectories) was fit as follows:

E(Yij) =βo +β1 (GWG)i + β2 (Race)i + β3 (Sex)i + β4 (Maternal Age)i + β5 (Prenatal Smoking)i + β6 (Income)i + β7 (Introduction to Solid Foods)i + β8 (Growth Measure at Birth)i (i.e. birth weight, birth length, weight-for-length at birth) + β9 (Infant Feeding)i + β10 (Time)ij + β11 $(tij-t^*)^+$ + β12 (Infant Feeding)i*(Time)ij + β13 (Infant feeding)i*$(tij-t^*)^+$)

Note, time was coded at months three (i.e., baseline), five, seven, and twelve.

To examine if infant feeding moderates the association between GWG and infant growth (aim 4), the model included an interaction term for infant feeding and GWG. The models for Aim 4 (i.e., the interaction of GWG and infant feeding on infant growth) were fit as follows:

$E(Y_{ij}) = \beta_o + \beta_1 (GWG)_i + \beta_2 (Race)_i + \beta_3 (Sex)_i + \beta_4 (Maternal\ Age)_i + \beta_5 (Prenatal\ Smoking)_i + \beta_6 (Income)_i + \beta_7 (Introduction\ to\ Solid\ Foods)_i + \beta_9 (Infant\ Feeding)_i + \beta_{10} (Time)_{ij} + \beta_{14} (Infant\ Feeding)_i * (GWG)_i$

Note: The growth measure at birth was excluded since it is on the causal pathway between GWG and infant growth. All analyses were carried out using SAS 9.3 (SAS Institute Inc., Cary, NC).

Institutional review board:

This secondary data analysis received Institutional Review Board exemption by the University of Maryland Institutional Review Board.

Chapter 5: Results

Descriptive statistics:

The analytic sample (N=1,939) was predominantly White (86%) and between 22-41 years of age (92%) (Table 4). Among my sample, inadequate GWG was least prevalent (18%), followed by adequate (37%), and excessive GWG (45%). And predominantly breastfed infants were most prevalent (56%), followed by predominantly formula fed (30%), and mixed fed (14%).

Table 4: Socio-demographic and maternal/ infant characteristics of study sample, 2007 IFPS II (N=1939)

		Gestational Weight Gain (GWG) Categories											
		Inadequate GWG (N=342)			*p*-value*	Adequate GWG (N=722)			*p*-value*	Excessive GWG (N=875)			*p*-value*
	Total Sample N (%)	Mixed Feeding N (%)	Predominantly Formula Fed N (%)	Predominantly Breastfed N (%)		Mixed Feeding N (%)	Predominantly Formula Fed N (%)	Predominantly Breastfed N (%)		Mixed Feeding N (%)	Predominantly Formula Fed N (%)	Predominantly Breastfed N (%)	
Maternal Characteristics													
Race/ethnicity					0.11*				0.17*				<0.01
White (Ref)	1669 (86)	39 (11)	98 (29)	154 (45)		76 (11)	169 (23)	378 (52)		96 (11)	235 (27)	424 (48)	
Black	77 (4)	6 (2)	8 (2)	7 (2)		4 (<1)	8 (1)	7 (<1)		12 (1)	13 (1)	12 (1)	
Hispanic	108 (6)	5 (1)	7 (2)	5 (1)		9 (1)	10 (1)	22 (3)		11 (1)	15 (2)	24 (3)	
Asian/ Pacific Islander	54 (3)	2 (<1)	2 (<1)	6 (2)		2 (<1)	6 (<1)	23 (3)		2 (<1)	3 (<1)	8 (<1)	
Other	31 (1)	1 (<1)	0 (0)	2 (<1)		1 (<1)	3 (<1)	4 (<1)		5 (<1)	8 (<1)	7 (<1)	
Age, years					0.13*				<0.01				<0.01*
18 to 21	131 (7)	6 (2)	7 (2)	7 (2)		7 (<1)	23 (3)	13 (2)		15 (2)	35 (4)	18 (2)	
22 to 31 (Ref)	1144 (59)	24 (7)	66 (19)	112 (33)		53 (7)	92 (13)	252 (35)		68 (8)	168 (19)	309 (35)	
32 to 41	642 (33)	23 (7)	41 (12)	52 (15)		30 (4)	79 (11)	162 (22)		41 (5)	70 (8)	144 (16)	
42 to 52	22 (1)	0 (0)	1 (<1)	3 (<1)		2 (<1)	2 (<1)	7 (1)		2 (<1)	1 (<1)	4 (<1)	
Family Income					<0.05				0.23				<0.01
<$19,999	236 (12)	11 (3)	28 (8)	16 (5)		12 (2)	24 (3)	38 (5)		22 (3)	44 (5)	41 (5)	
$20,000-39,000	573 (30)	12 (4)	35 (10)	60 (18)		24 (3)	63 (9)	118 (16)		31 (3)	90 (10)	140 (16)	
$40,000-59,000	472 (24)	11 (3)	28 (8)	46 (13)		24 (3)	38 (5)	102 (14)		25 (2)	56 (6)	142 (16)	
$60,000-99,000 (Ref)	496 (26)	15 (4)	20 (6)	39 (11)		22 (3)	48 (7)	139 (19)		33 (4)	62 (7)	118 (13)	
≥$100,000	162 (8)	4 (1)	4 (1)	13 (4)		10 (1)	23 (3)	37 (5)		15 (2)	22 (3)	34 (4)	
Prenatal Smoking					<0.01*			<0.01*					<0.01
0 cigarettes per day (Ref)	1784 (92)	45 (13)	94 (27)	170 (50)		82 (11)	167 (23)	421 (58)		10 7 (12)	243 (28)	455 (52)	
1-10 cigarettes per day	110 (6)	6 (1)	16 (5)	2 (<1)		7 (<1)	20 (3)	8 (1)		13 (1)	22 (3)	16 (2)	
11-20 cigarettes per day	45 (2)	2 (<1)	5 (<1)	2 (<1)		3 (<1)	9 (1)	5 (<1)		6 (<1)	9 (1)	4 (<1)	
Infant Characteristics													
Sex of Infant					0.61				0.76				0.30
Boy	943 (49)	24 (7)	54 (16)	90 (26)		43 (6)	99 (14)	207 (29)		69 (8)	134 (15)	223 (25)	
Girl (Ref)	996 (51)	29 (8)	61 (18)	84 (25)		49 (7)	97 (13)	227 (31)		57 (7)	140 (16)	252 (29)	
Introduction to Solid Foods					<0.01				<0.01				<0.01
Yes	462 (24)	28 (8)	43 (13)	20 (6)		42 (6)	69 (10)	33 (5)		68 (8)	97 (11)	62 (7)	
No (Ref)	1477 (76)	25 (7)	72 (21)	154 (45)		50 (7)	127 (18)	401 (56)		58 (7)	177 (20)	413 (47)	

*denotes Fisher's Exact Test was used to estimate the p-value to improve precision. Fisher's Exact Test is the preferred statistical procedure when one or more of the cells is < 5.

Statistical significance at p<0.05

Note: all other p-value estimates were based on Chi Square tests.

Table 5a displays the percentage of infant growth gain during infancy for each feeding type stratified by GWG.

Table 5a: Percentage of infant growth gain during infancy

	Inadequate GWG			**Adequate GWG**			**Excessive GWG**		
	Mixed	**Formula**	**Breastfed**	**Mixed**	**Formula**	**Breastfed**	**Mixed**	**Formula**	**Breastfed**
Weight	192%	195%	170%	180%	192%	169%	186%	186%	163%
Length	53%	46%	45%	50%	49%	48%	50%	50%	47%
Weight-for-Length	87%	106%	84%	92%	92%	84%	95%	95%	82%

In the bivariate table, a*cross all* GWG groups, breastfed infants gained the least amount of weight, length, and weight-for-length of all feeding groups. *Across all* GWG groups, particularly adequate and excessive GWG, feeding type does not have a strong association with length. Infants in the inadequate GWG group gained the most weight during infancy independent of feeding type. Formula fed and breastfed infants in the excessive GWG group gained the least amount of weight compared to the respective feeding types within the other GWG groups.

Table 5b displays the values for continuous growth variables at months three, five, seven, and twelve by GWG category and feeding type. The following highlights select descriptive statistics for each GWG category by feeding type.

Inadequate GWG:

Within the inadequate GWG group, at five months, the mixed-fed infants were heaviest (15.19 lbs.), followed by predominantly breastfed infants (14.60 lbs.), and predominantly formula-fed infants (14.31 lbs.), (p=0.02). At five months predominantly breastfed were the shortest (24.75 in.), followed by predominantly formula fed (25.00 in.), and mixed fed (26.00 in.). At seven months, the weight-for-length for breastfed was (0.62 in./lbs.), formula fed (0.65 in./lbs.), and mixed fed (0.66 in./lbs.) (p=0.03).

Adequate GWG:

Within the adequate GWG group, at five months, the median weight for predominantly breastfed (14.50 lbs.) was less than that of predominantly formula fed (15.13 lbs.) and mixed fed (15.38 lbs.) (p =0.01). Infant length was not significant during infancy. The median weight-for-length at five months for breastfed was (0.58 in./lbs.), formula fed (0.60 in./lbs.), and mixed fed (0.62 in./lbs.) (p <0.01).

Excessive GWG:

Within the excessive GWG group, at five months, the median weight for predominantly breastfed (15.00 lbs.) and predominantly formula fed (15.00 lbs.) was less than that of mixed fed (15.16 lbs.) (p =0.02). The median length at month twelve was the least for breastfed infants (29.50 in.), followed by formula fed (30.00 in.) and mixed fed (30.00 in.) (p =0.05). At five months, the median weight-for-length for breastfed was (0.60 in./lbs.), formula fed (0.61 in./lbs.), and mixed fed (0.60 in./lbs.) (p <0.01).

We would have expected the growth of mixed fed infants to fall somewhere between that of formula fed and breastfed infants. However, since this was not the case, a post hoc analysis was conducted to better understand the growth of mixed fed infants. This analysis indicated that on average the mixed fed infants' diet consisted of 50% formula and 38% breast milk. Furthermore, by month two and three 32% and 48% of the mixed fed infants were introduced solid food. Whereas, 19% of formula fed and 4% of breastfed infants received solid food at month two and 32% of formula fed and 9% of breastfed infants received solid food by month three. Mixed fed infants were introduced solid foods earlier than breastfed and formula fed infants. It is possible that the early introduction of solid foods in the mixed fed infants' diet contributed to greater weight and length gains.

Table 5b: Infant Growth Variables by GWG Category and Infant Feeding Type, 2007 IFPS II (N=1939)

	Gestational Weight Gain (GWG) Categories											
	Inadequate GWG (N=342)			*p*-value	Adequate GWG (N=722)			*p*-value	Excessive GWG (N=875)			*p*-value
	Mixed Feeding	Predominantly Formula Fed	Predominantly Breastfed		Mixed Feeding	Predominantly Formula Fed	Predominantly Breastfed		Mixed Feeding	Predominantly Formula Fed	Predominantly Breastfed	
	Median [Q1,Q3]											
Weight (lbs.)												
Birth	7.44 [6.88, 8.38]	7.13 [6.69, 7.75]	7.35 [6.75, 8.0]	0.02	7.60 [6.94, 8.19]	7.31 [6.56, 8.00]	7.56 [6.94, 8.19]	0.01	7.88 [7.19, 8.38]	7.75 [7.13, 8.44]	7.88 [7.13, 8.63]	0.19
Month 3	11.94 [11.00, 13.13]	11.63 [10.88, 12.50]	12.00 [10.47, 13.56]	0.11	11.88 [10.88, 13.00]	12.00 [11.00, 13.16]	12.13 [11.00, 13.38]	0.45	12.44 [11.25, 13.56]	12.50 [11.31, 13.50]	12.35 [11.19, 13.69]	0.70
Month 5	15.19 [14.13, 16.69]	14.31 [13.38, 15.38]	14.60 [13.00, 16.00]	0.02	15.38 [14.13, 16.31]	15.13 [13.88, 16.88]	14.50 [13.38, 16.13]	0.01	15.16 [13.72, 16.66]	15.00 [14.25, 17.00]	15.00 [13.50, 16.31]	0.02
Month 7	17.97 [16.60, 19.47]	17.07 [15.85, 18.35]	16.56 [14.88, 18.25]	0.02	17.75 [16.44, 20.00]	17.38 [16.00, 19.25]	16.94 [15.25, 18.44]	<0.01	18.06 [16.50, 20.00]	17.94 [16.94, 19.50]	17.19 [15.75, 18.63]	<0.01
Month 12	21.75 [20.25, 23.75]	21.00 [19.25, 22.25]	19.85 [18.32, 22.44]	0.01	21.25 [19.88, 23.00]	21.31 [19.63, 23.50]	20.31 [19.00, 22.31]	<0.01	22.50 [21.13, 24.00]	22.19 [20.38, 24.00]	20.75 [19.44, 22.38]	<0.01
Length (in.)												
Birth	20.0 [19.50, 21.00]	20.0 [19.25, 20.00]	20.0 [19.25, 20.50]	0.14	20.0 [19.50, 20.75]	20.0 [19.00, 20.75]	20.0 [19.50, 20.75]	0.48	20.0 [19.25, 20.50]	20.0 [19.50, 21.00]	20.13 [19.50, 21.00]	0.01
Month 3	23.00 [22.25, 24.00]	23.0 [21.63, 23.50]	23.0 [22.0, 24.0]	0.19	23.00 [22.00, 24.00]	23.00 [22.00, 24.00]	23.00 [22.25, 24.00]	0.39	23.25 [22.75, 24.00]	23.00 [22.00, 24.00]	23.00 [22.25, 24.00]	0.61
Month 5	26.00 [25.00, 27.00]	25.00 [24.00, 26.00]	24.75 [23.00, 25.50]	<0.01	24.75 [24.00, 26.00]	25.00 [24.00, 26.00]	25.00 [24.00, 26.00]	0.56	25.00 [24.00, 26.00]	25.00 [24.00, 26.00]	25.00 [24.00, 26.00]	0.97
Month 7	27.00 [26.00, 28.00]	26.75 [26.00, 27.50]	26,00 [25.00, 27.00]	0.08	26.00 [25.00, 27.50]	26.50 [25.00, 27.75]	26.50 [26.00, 27.50]	0.90	27.00 [26.00, 28.00]	26.75 [26.00, 28.00]	26.50 [25.50, 27.25]	0.08
Month 12	30.50 [29.50, 31.00]	29.13 [28.88, 30.25]	29.00 [28.00, 30.00]	0.02	30.00 [29.00, 31.00]	29.75 [28.50, 30.75]	29.50 [28.50, 30.00]	0.22	30.00 [29.00, 31.00]	30.00 [28.00, 31.00]	29.50 [28.50, 30.50]	0.05
Weight-for-Length (lbs./in.)												
Birth	0.38 [0.35, 0.41]	0.36 [0.34, 0.38]	0.37 [0.34, 0.40]	0.01	0.38 [0.35, 0.40]	0.37 [0.34, 0.40]	0.38 [0.35, 0.41]	0.02	0.39 [0.37, 0.42]	0.38 [0.35, 0.41]	0.39 [0.36, 0.42]	0.23
Month 3	0.51 [0.47, 0.56]	0.51 [0.48, 0.55]	0.52 [0.47, 0.57]	0.58	0.52 [0.47, 0.56]	0.52 [0.48, 0.57]	0.52 [0.49, 0.57]	0.42	0.53 [0.50, 0.59]	0.53 [0.49, 0.58]	0.53 [0.49, 0.58]	0.85
Month 5	0.60 [0.56, 0.62]	0.58 [0.54, 0.63]	0.59 [0.54, 0.65]	0.45	0.62 [0.58, 0.67]	0.60 [0.57, 0.66]	0.58 [0.54, 0.63]	<0.01	0.60 [0.55, 0.66]	0.61 [0.57, 0.66]	0.60 [0.55,0.64]	0.01
Month 7	0.66 [0.61, 0.74]	0.65 [0.62, 0.69]	0.62 [0.57, 0.68]	0.03	0.68 [0.63, 0.75]	0.66 [0.62, 0.72]	0.64 [0.58, 0.69]	0.02	0.67 [0.62, 0.74]	0.67 [0.62, 0.72]	0.65 [0.60, 0.70]	<0.01
Month 12	0.71 [0.70, 0.76]	0.74 [0.69, 0.81]	0.68 [0.64, 0.75]	<0.01	0.73 [0.67, 0.79]	0.71 [0.67, 0.80]	0.70 [0.65, 0.77]	0.03	0.76 [0.73, 0.82]	0.74 [0.69, 0.80]	0.71 [0.67, 0.77]	<0.01

Statistical significance at $p<0.05$

Table 6 shows the association between GWG and infant growth controlling for demographic variables (race/ethnicity, income, mother's age, sex of the infant), introduction to solid foods, and maternal prenatal smoking (top panel). In addition, table 6 displays the association between infant feeding with infant weight, length, and weight-for-length during infancy controlling for the aforementioned demographic variables, GWG, introduction to solid foods, and maternal prenatal smoking (bottom panel). The infant feeding models (bottom panel) also include birth weight when predicting weight, birth length when predicting length, and weight-for-length at birth when predicting weight-for-length.

Aim 1: Determine at which point in time the association between GWG and three conditional growth outcomes is statistically significant.

Within all GWG groups, significant differences in all growth outcomes were first apparent at three months of age. At three months of age, compared to the adequate GWG group (12.19 lbs.), infants in the inadequate GWG group were lighter (-0.24 lbs.; 95% CI: -0.36, -0.12), while infants in the excessive GWG group were heavier (0.28 lbs.; CI: -0.19, 0.38). At three months, compared to the adequate GWG group (23.07 in.), infants in the inadequate GWG group were shorter (-0.13 in.; 95% CI: -0.23, -0.03) while infants in the excessive GWG group were longer (0.09 in.; 95% CI: 0.01, 0.17). At three months, compared to the adequate GWG group (0.53 lbs./in.), infants in the inadequate GWG group weight-for-length was less (-0.01 lbs./in.; 95% CI: -0.01, -0.01) and the excessive GWG group was more (0.01 lbs./in.; 95% CI: 0.01, 0.01).

Aim 2: Determine at which point in time the association between *feeding type* and three conditional growth outcomes (i.e. length, weight, and weight-for-length) becomes statistically significant.

A significant difference in feeding type and weight was first apparent at five months of age (Table 6). At five months, compared to breastfed infants (14.81 lbs.), both formula fed (0.38 lbs.; 95% CI: 0.26, 0.50) and mixed fed infants (0.37 lbs.; 95% CI: 0.21, 0.53) were heavier.

At seven months of age, a significant difference in infant length by feeding type was first apparent. At month seven, compared to breastfed infants (26.22 in.) formula fed (0.24 in.; 95% CI: 0.10, 0.39) and mixed fed infants (0.47 in. 95% CI: 0.27, 0.67) were longer.

A significant difference in infant weight-for-length by feeding type was first apparent at twelve months of age. At twelve months, compared to breastfed infants (0.71 lbs./in.), the weight-for-length for both formula fed (0.03 lbs./in; 95% CI: 0.03, 0.04) and mixed fed infants (0.04 lbs./in.; 95% CI: 0.03, 0.04) was more.

Table 6: Regression models of the association of GWG and infant feeding type with weight, length, and weight-for-length during infancy, 2007 IFPS II (N=1939)

	Months:				**Months:**				**Months:**			
	3 (N=1900)	**5 (N=1596)**	**7 (N=1494)**	**12 (N=1312)**	**3 (N=1612)**	**5 (N=1284)**	**7 (N=1075)**	**12 (N=928)**	**3 (N=1612)**	**5 (N=1284)**	**7 (N=1075)**	**12 (N=928)**
	Weight (lbs.)				**Length (in.)**				**Weight-for-length (lbs./in.)**			
GWG[1]												
Adequate	--	--	--	--								
Inadequate	-0.24 (-0.36, -0.12)*	-0.37 (-0.52, -0.22)*	-0.26 (-0.44, -0.09)*	-0.35 (-0.57, -0.14)*	-0.13 (-0.23, -0.03)*	-0.29 (-0.42, -0.16)*	-0.06 (-0.25, 0.13)	-0.59 (-0.82, -0.37)*	-0.01 (-0.01, -0.01)*	-0.01 (-0.01, -0.01)*	-0.01 (-0.04, 0.03)	0.01 (-0.01, 0.01)
Excessive	0.28 (0.19, 0.38)*	0.16 (0.04, 0.28)*	0.30 (0.17, 0.44)*	0.49 (0.33, 0.66)*	0.09 (0.01, 0.17)*	0.03 (-0.07, 0.13)	-0.02 (-0.16, 0.12)	0.17 (0.10, 0.33)*	0.01 (0.01, 0.01)*	0.01 (-0.01, 0.01)	0.05 (0.02, 0.07)*	0.01 (0.01, 0.02)*
Feeding Type[2 3]												
Breastfed	--	--	--	--								
Formula Fed	-0.04 (-0.13, 0.05)	0.38 (0.26, 0.50)*	0.70 (0.56, 0.83)*	1.00 (0.84, 1.17)*	-0.09 (-0.16, -0.01)*	0.10 (-0.01, 0.20)	0.24 (0.10, 0.39)*	0.20 (0.03, 0.37)*	-0.01 (-0.01, 0.01)	0.02 (0.01, 0.02)*	0.04 (0.01, 0.07)*	0.03 (0.03, 0.04)*
Mixed Fed	-0.05 (-0.17, 0.08)	0.37 (0.21, 0.53)*	0.93 (0.74,1.12)*	1.44 (1.21, 0.68)*	0.10 (-0.01, 0.20)	0.28 (0.14, 0.43)*	0.47 (0.27, 0.67)*	0.78 (0.55, 1.02)*	-0.01 (-0.01, -0.01)*	0.01 (-0.01, 0.01)	0.02 (-0.02, 0.06)	0.04 (0.03, 0.04)*

Note: Asterisk denotes statistical significance $p<0.05$

[1] GWG models include demographic variables (race/ethnicity, income, mother's age, sex of the infant), introduction to solid foods, and maternal prenatal smoking.

[2] Infant feeding models include demographic variables (race/ethnicity, income, mother's age, sex of the infant), GWG, introduction to solid foods, and maternal prenatal smoking.

[3] The infant feeding models include birth weight when predicting weight, birth length when predicting length, and weight-for-length at birth when predicting weight-for-length.

Rate of growth:

Aim 3: Describe the change in the growth trajectory by feeding type.

Table 7 displays the rate of change in the three growth outcomes at 3-5 months and at 5-12 months, and the difference in the rate of growth between these two time periods. To describe the change in growth trajectory by feeding type, month five was selected as the comparison point. The linear combination of coefficients for the slopes are also presented in Table 7.

Table 7: Slopes (coefficients (β) for their calculation) estimating change in growth comparing months three to five with months five to twelve, 2007 IFPS II (N=1939)

Feeding Type	Weight Trajectory (lbs./mth.)		Difference in Weight Trajectories (lbs./mth.)	Length Trajectory (in./mth.)		Difference in Length Trajectories (in./mth.)	Weight-for-Length Trajectory (lbs./in.)		Difference in Weight-for-Length Trajectories (lbs./in.)
	Months 3-5	Months 5-12		Months 3-5	Months 5-12		Months 3-5	Months 5-12	
Predominantly Breastfed	1.37 ($\beta3$)	0.82 ($\beta3 + \beta4$)	-0.55* ($\beta4$)	0.91 ($\beta3$)	0.60 ($\beta3 + \beta4$)	-0.30* ($\beta4$)	0.04 ($\beta3$)	0.02 ($\beta3 + \beta4$)	-0.02* ($\beta4$)
Predominantly Formula Fed	1.63 ($\beta3 + \beta6$)	0.91 ($\beta3 + \beta4 + \beta6 + \beta8$)	-0.72* [1] ($\beta4 + \beta8$)	0.99 ($\beta3 + \beta6$)	0.61 ($\beta3 + \beta4 + \beta6 + \beta8$)	-0.38* ($\beta4 + \beta8$)	0.05 ($\beta3 + \beta6$)	0.02 ($\beta3 + \beta4 + \beta6 + \beta8$)	-0.03* ($\beta4 + \beta8$)
Mixed Fed	1.67 ($\beta3 + \beta5$)	0.97 ($\beta3 + \beta4 + \beta5 + \beta7$)	-0.70* ($\beta4 + \beta7$)	0.95 ($\beta3 + \beta5$)	0.66 ($\beta3 + \beta4 + \beta5 + \beta7$)	-0.29* ($\beta4 + \beta7$)	0.05 ($\beta3 + \beta5$)	0.03 ($\beta3 + \beta4 + \beta5 + \beta7$)	-0.03* ($\beta4 + \beta7$)

Statistical significance at $p<0.05$

* denotes statistical significance for within group differences

[1] denotes statistical significance for comparison of predominantly formula fed with predominantly breastfed infants (i.e. between group differences)

The difference in weight trajectories is considerably less among predominantly breastfed (0.55 lbs./mth.) relative to the weight trajectories of predominantly formula fed (0.72 lbs./mth.) and mixed fed (0.70 lbs./mth.) infants. The difference in slopes describing the length trajectories was highest among formula fed (0.38 in./mth.) compared to breastfed (0.30 in./mth.) and mixed fed infants (0.29 in./mth.). Also, the difference in slopes describing the weight-for-length trajectory by feeding type was fairly stable for breastfed (0.02 lbs./in.), formula fed (0.03 lbs./in.), and mixed fed (0.03 lbs./in.) infants. See Appendix C and Appendix D for full calculations.

Looking at the difference between feeding groups, formula fed infants weighed 0.17 lbs. more ($p < 0.01$) than breastfed infants. The comparisons of length and weight-for-length trajectories between feeding groups were not significant.

Aim 4: To examine if infant feeding moderates the association between GWG and infant growth.

The interaction between GWG and infant feeding was significant when predicting weight ($p < 0.05$) and marginally significant when predicting length ($p = 0.06$). The interaction did not retain its significance when weight-for-length was the outcome. The estimates for the main effect and interaction of infant feeding and GWG are included in Appendix D for reference.

Chapter 6: Discussion/Conclusion

Health behaviors during pregnancy and feeding during infancy are of critical importance to the infant growth trajectory. Survival during infancy depends on an infant's ability to achieve developmental milestones, one of which is to maintain adequate growth.[1] This analysis set out to better understand the independent and synergistic effects of pre-pregnancy BMI, GWG, and infant feeding on growth during infancy.

In this sample, consistent with other studies, infant weight evinced an independent association with GWG;[18,19, 78–80] in our sample, this association is evident throughout infancy. As expected, infants of mothers with inadequate GWG weighed less and infants of mothers with excessive GWG weighed more than infants of mothers with adequate GWG. This consistent association between maternal and infant weight gain in all likelihood reflect the intertwined underlying physiologic processes driving growth.

There was a weak association between GWG and length. Although an association between GWG and infant length was apparent at month three and twelve, this association was not consistently evident throughout infancy. For the most part, infants born to mothers with inadequate GWG weighed less and were shorter while infants born to mothers with excessive GWG weighed more and were longer compared to infants born to mothers with adequate GWG.

The difference in infant weight between the inadequate and excessive GWG groups appear to be increasing over time with the greatest difference in weight at 12 months. Perhaps, additional factors, such as infant feeding are contributing to this disparity. Infant weight disparities by GWG group highlight the importance of maintaining a healthy weight during pregnancy.

The ratio of weight-for-length demonstrates a difference in infant proportionality by GWG category at month three; however, this difference is too small to be clinically meaningful. At seven months, infants in the excessive GWG group had the greatest weight-for-length ratio, reflecting disproportionate growth. The differences in growth among infants born to mothers who gained excessive, inadequate, or adequate weight during pregnancy may be attributed to the underlying metabolic processes or differences in infant feeding behaviors. In addition to GWG, infant feeding is an important consideration when assessing infant growth outcomes.

Consistent with other studies, infant weight is associated with feeding type as well.[32,35,92,93] In this study sample, by month five, there was an independent association between infant feeding and weight. Consistent with other studies, the association between infant feeding and infant length was inconsistent.[32] Lastly, the weight-for-length difference was too small to be clinically meaningful. We can conclude from this analysis that the most consistent association among the growth measures is between infant feeding and infant weight.

The weight trajectory of breastfed infants is steadier than that of formula fed and mixed fed infants highlighting the protective effect of breastfeeding on excessive weight gain. Furthermore, the within group difference in slopes was greatest among formula fed infants followed by mixed fed infants indicating a faster rate of weight gain. The higher weights of formula and mixed fed infants may result in a negative weight trajectory over time. In addition, the within group difference of length slopes is greatest among formula fed infants; however, infant length was similar between feeding groups. Lastly, in terms of proportionality, the weight-for-length trajectory is similar for all feeding groups with breastfed infants exhibiting the slowest measure of weight-for-length. Although the selection of a change point is somewhat arbitrary, the infant weight regression models displayed the most consistent association at each time point with notable differences in weight for both GWG and infant feeding at month five.

All feeding types experienced a significant rate of change before and after the month five change point. It is also important to note that the greatest increase in growth trajectories was from months three to five among all feeding groups. Furthermore, there appears to be a slowing of growth from months five to twelve compared to months three to five among all feeding groups. This may indicate that a critical window for growth occurs early in infancy.

Lastly, pre-pregnancy BMI/GWG modified the association between infant feeding and infant growth. Additional research is needed to improve our understanding of the relationship between pre-pregnancy BMI/GWG, infant feeding, and infant growth. Pregnancy and infancy are two distinct windows in which behavior modification can lead to improved growth outcomes.[118]

Critical periods:

The gestational period has been referred to as a critical period consisting of windows of susceptibility, where an exposure may have a greater effect at specific times during gestation. Exposures during these windows of susceptibility have been linked to a wide array of health outcomes including cardiovascular disease, type 2 diabetes, osteoporosis, depressive disorders, and certain cancers.[87,42] Infancy is also an important period of growth and development.[37,119–122] Infancy may be an additional critical period where early infant feeding practices play an integral role in establishing metabolic processes and growth patterns.[123,124] Both human and animal studies suggest that metabolic programming during infancy can influence later metabolic processes.[122,125,126] Organ development continues post-birth to enable the infant to adapt to their new environment.[127] This period of developmental plasticity increases the infant's susceptibility to maladaptive programming, thereby predisposing the infant to suboptimal growth. The first six months of life may be considered a vulnerable period in which metabolic programming may have a permanent effect on the growth of the individual.[127] Researchers must focus on both the gestational and infancy periods; as suboptimal growth process in these early stages of human development may equate to the early antecedents of adult disease.

Life course theory:

The life course perspective posits that health and disease develop across the life span with an emphasis on the key role of early experiences.[128] Life course theory challenges traditional biomedical models and offers a new way of understanding the etiology of disease.[128] Preventive efforts should not focus on simple exposure outcome relationships or on a single life stage. Rather, the health phenotype is both dynamic and complex and can have major implications to both short and long term health.

Life course epidemiology represents a convergence of sociological and psychological approaches to understanding human development.[129] Theories about the fetal origins or the developmental origins of disease are widespread. Notably, David

Barker proposed that fetal programming during gestation results in irreversible changes to the fetus' body structure, function, and metabolism and that suboptimal fetal growth can predispose an individual to adult disease. [87, 129] Others have suggested that under nutrition during gestation followed by a plentiful food source post birth results in a mismatch between the metabolic processes and the nutritional environment predisposing an individual to metabolic syndrome, insulin resistance and obesity.[4] Maternal and child health issues are clearly intertwined; as such public health professionals must assess maternal, infant, and child growth trends and target interventions before, during, and beyond pregnancy.

Pre-pregnancy BMI and GWG trends:

In the U.S. pre-pregnancy maternal obesity has increased significantly over the past 15 years.[68] This rise in average maternal pre-pregnancy BMI is associated with an increase in average birth weights in the U.S.[68] Furthermore, approximately one-third of all pregnant women in the U.S. are obese.[8] Obese pregnant women give birth to infants who are also at an increased risk of excessive growth or growth rates that are higher than standardized growth targets.[130] Post-birth, the rate of growth is an important consideration when assessing infant health since it is representative of the underlying metabolic processes. Current U.S. birth weight trends appear to be reflective of the population level increases in maternal pre-pregnancy BMI and GWG. These weight trends continue from pre-pregnancy, pregnancy, birth, childhood and into adolescence.

This shift in the U.S. population's weight distribution has serious health implications at the population level. Some of the leading causes of death are obesity-related; such as heart disease, stroke, type 2 diabetes and certain types of cancer. The long-term health effects of obesity highlights the importance of developing early interventions; as early as preconception, to prevent childhood obesity at the earliest stages of development. In addition to maternal factors and their influence on growth, infant feeding behaviors play an important role establishing growth trajectories as well.

Infant feeding trends:

Despite national recommendations to exclusively breastfeed through six months of age, and the known nutritional, immunological, psychological, and developmental benefits of breastfeeding; formula feeding is highly prevalent in our society.[28,30] In the U.S. in 2009, 76.9% of women who give birth initiated breastfeeding but only 16.3% exclusively breastfed through six months of age. [131,132] The prevalence of 'any breastfeeding' at six months and twelve months is 47.2% and 25.5%, respectively.[131] Although breastfeeding rates have improved since 2001, exclusive breastfeeding rates are low and we continue to fall short of the national targets. [28, 30, 131]

Maternal obesity and breastfeeding:

High pre-pregnancy BMI and GWG can also influence breastfeeding practices.[133] Overweight/obese women are more likely to experience delayed milk production as compared to normal weight women.[134] Prolactin is the hormone responsible for milk production. Obesity lowers prolactin secretion which thereby delays lactogenesis.[135] In addition, there may be a diminished prolactin response to suckling among overweight/obese women.[135] A low milk supply can then influence infant suckling duration and consequently influence the breastfeeding dose. Furthermore, there may be mechanical difficulties of latching and proper positioning of the infant among obese mothers.[136]

Feeding mode and infant growth:

Another consideration when assessing infant feeding is whether an infant is nursed or bottle-fed (i.e., feeding mode). Nursed infants must actively suckle to consume milk, whereas bottle-fed infants rely on the caregiver's control of the amount of feeding.[137] Consequently, bottle fed infants, regardless of whether the bottle contains formula or expressed milk, may have an inhibited ability to self-regulate their intake and may consume a greater quantity of milk compared to nursed infants.[137] Moreover, nursed infants may perceive the difference in taste of foremilk and hind milk, which may be a cue to stop feeding; whereas breast milk given by bottle is mixed without any indication that the end of a feed is impending. Bottle-feeding may ultimately result in poor self-regulation and overconsumption.[137] The protective effects of breastfeeding on growth may be attributed to the constituents of breast milk and the reduced likelihood of overconsumption.[34]

Infant feeding measurement issues:

Another important consideration when assessing infant feeding is the parameterization of the infant feeding variable. A universally agreed upon standard for infant feeding measurement does not currently exist. The WHO defines exclusive breastfeeding as "breastfeeding or formula feeding while giving no other food or liquid, not even water."[29] However, few studies report this exact definition as too few infants are fed exclusively breast milk or formula.[138] Furthermore, this definition includes expressed milk; thereby neglecting to account for the mode of delivery. Predominant breastfeeding is another term supported by WHO as a crude estimate of the primary source of nutrition or a large proportion of breast milk to total feeds.[29] The terms full breastfeeding (i.e., exclusive, almost exclusive), partial breastfeeding (i.e., high, medium, low), and token breastfeeding (i.e., minimal, occasional, irregular) are commonly used in an effort to accurately classify breastfeeding patterns as well.[139]

To reduce ambiguity, standard definitions of infant feeding have been introduced but have not been widely accepted.[107] Infant feeding categories, based on a proportion, may be more representative of actual feeding practices than all or none categorizations. Future research should aim to adopt a single set of definitions to harmonize terminology.

Infant feeding patterns:

Another challenge in the assessment of infant feeding is the fact that feeding type, duration, and quantity can vary over time. Caregivers may supplement breastfeeding at the hospital and then exclusively breastfeed thereafter, others may initiate breastfeeding and then switch to formula feeding, and some individuals practice mixed feeding involving both breast milk and formula. The protective effects of breastfeeding are likely dose-related and therefore precise measures of infant feeding patterns are necessary to improve the validity of the findings.

Measures of infant growth:

Although the growth of breastfed and formula fed infants may differ, one must also consider that infants that are breastfed for 12 months may be leaner than formula fed infants.[140] Consequently, weight and length alone may be insufficient for assessing the health of the infant. Body composition, the measure of fatness and fat-free mass, can be assessed with a full body DXA scan.[141] Serial monitoring of body composition may provide insights on underlying physiologic processes and provide a more precise measure of infant growth.[26]

Study strengths:

The IFPS II population enrolled a nationally-based sample of women in their third trimester of pregnancy. The IFPS II offers detailed information on infant feeding and health on a large sample of U.S. infants. All survey questions underwent extensive testing prior to study implementation.[41] The high frequency of questionnaires during infancy allowed for detailed analyses of infant food intake. As previously mentioned, standard infant feeding terminology does not exist. With this in mind, the food frequency questions were intentionally broad which enabled me to capture the heterogeneity of infant feeding behaviors while allowing recoding and parameterization of infant feeding variables to better address my research questions.

Study limitations:

Although the questionnaires were administered approximately monthly, there was some variability in age when the questionnaires were completed. First, some participants enrolled in the study late and the birth screener and neonatal questionnaire were mailed together resulting in infants being older than the target age.[41] In addition, questionnaires were not always completed immediately upon receipt and the questionnaires were mailed twice monthly independent of the age of the infant. However, the median age of the study sample matched the target age of the infant.[41] Although participants were solicited nation-wide, the study population was not representative of the U.S. population. Furthermore, participants were recruited through a consumer-based panel where individuals volunteered to complete a series of surveys on a variety of topics. This resulted in a sample with an overrepresentation of white women of higher socioeconomic status (SES). Ensuring a high response rate on a high frequency of questionnaires was deemed a higher priority than obtaining a representative sample; as women who volunteered to complete consumer-based panel studies were more likely to remain in the study. However, this study was focused on physiologic outcomes, therefore it is reasonable to conclude that the findings are valid. Another limitation of the IFPS is that the food frequency data only indicated the number of daily feeds and not the amount consumed or the duration of the feed. Therefore, daily feeds were used as a proxy for dietary intake. Lastly, the data were based on retrospective maternal report in the last seven days and therefore may be subject to error.

For the purpose of this analysis, individuals were excluded if they were missing all covariates and all growth outcomes of interest. Therefore, individuals with some growth outcomes were included in the sample. Excluding individuals may limit generalizability as complete cases may differ from the incomplete cases. A post hoc analysis indicated that select demographics of those excluded from this study were statistically different from the study sample. Although this limits generalizability, the findings are reasonable within this sample. It would be interesting to explore if there is an association between GWG, infant feeding and infant growth stratified by select demographics. In addition, it is unknown whether infant feeding decisions are in response to growth status (i.e., reverse causality). Additional survey questions are necessary to explore this possibility. Lastly, beyond feeding type in early infancy, the timing of the introduction of solid foods and nutritional quality of the foods may also contribute to differences in growth. Family food habits may be driving growth differences. This study only took into account if solid foods were introduced during the infant feeding exposure window. Future analyses could incorporate the timing of the introduction of solid foods throughout infancy and take into consideration the family context.

Policy implications:

National level recommendations on GWG and infant feeding provide a benchmark for improving the health of mothers and infants. Healthy People 2020 targets on pre-pregnancy BMI, GWG, breastfeeding, and lactation support programs, all compliment national level recommendations and guidelines.[31] In addition to achieving a healthy weight prior to and during pregnancy, returning to a healthy weight postpartum is also important to improve intergenerational weight trends.[142] Breastfeeding can assist women in returning to a normal BMI postpartum; as breastfeeding has been associated with an improved ability to limit weight retention postpartum.[143] It is not surprising that recent focus has been on improving breastfeeding rates given the benefits to both mothers and infants.

In an effort to meet the Healthy People 2020 goals, numerous breastfeeding promotion guides have been disseminated broadly including the Surgeon General's Call to Action to Support Breastfeeding,[28] Baby Friendly Hospital Initiative: Ten steps to successful breastfeeding,[144] CDC's Support for Breastfeeding in the Workplace,[145] and Strategies to Prevent Obesity and Other Chronic Diseases: The CDC Guide to Strategies to Support Breastfeeding Mothers and Babies.[146] This last CDC resource highlights the need to promote breastfeeding as an obesity prevention strategy.

States rely on evidence-based guidelines and national level data to inform the development of local programs and interventions. National and state level data provide valuable information on maternal weight and infant feeding trends and enable cross-state comparisons so that states can be responsive to identified needs. For example, the results of CDC's National Immunization Survey showed that New York had the highest proportion of breastfed infants who were receiving supplemental feeding with formula by 2 days of age.[147] To address this issue, officials used state-level infant feeding data to rank state hospitals on three breastfeeding indicators: initiation, exclusivity, and formula supplementation of breastfed infants in the hospital.[148] The hospitals were then ranked and each hospital was notified as to how they compare with other hospitals in the state. The data were also shared with all maternity patients and posted on the New York State Department of Health Website.[148] The state of New York also formed a quality improvement learning collaborative among twelve state hospitals and made available breastfeeding management courses.[148] Establishing learning collaboratives and training teams can contribute to a paradigm shift toward a breastfeeding friendly environment.

Breastfeeding barriers:

Although evidence consistently renders breastfeeding as the gold standard of nutrition, actual infant feeding practices vary by race, ethnicity, income status, and other demographic variables. The workplace is often cited as a barrier to breastfeeding.[149] Working mothers are less likely to initiate breastfeeding, and they breastfeed for a shorter period of time in comparison to non-working mothers.[28] Often times, working mothers choose formula over breast milk for convenience. Job type can also influence the feasibility of breastfeeding. A recent study found that women returning to a professional job as compared to a sales or technical job had a longer duration of breastfeeding.[150] Job demands can interfere with a woman's ability to take breastfeeding breaks. Workplace barriers present a logistical challenge to improving breastfeeding rates.

Low-income mothers face additional emotional, physical, and logistical challenges that often make it necessary to turn to formula as a convenient alternative to breastfeeding. [30,151,149] Women of lower socioeconomic status (SES) are at a distinct disadvantage for adopting breastfeeding practices. In comparison to higher paid professional positions, women of lower SES tend to have little to no flexibility in the workplace to breastfeed, may find breast pump equipment unaffordable, and may not have a private space to accommodate breastfeeding or to express milk.

Balancing breastfeeding and work is a major challenge across the SES gradient. Women who return to work shortly after giving birth may result in early breastfeeding cessation. Instituting a national policy for paid maternity leave could result in improvements in breastfeeding initiation and duration.

Infant feeding practices are also influenced by societal norms and beliefs about culturally acceptable breastfeeding behaviors. Intervention programs must take into account the wide range of personal views on infant feeding. Changing cultural beliefs and behaviors is a formidable challenge. Individual behaviors are more likely to be influenced by friends and families than medical practitioners or the existence of national policies. However, both macro and micro level initiatives are necessary to overcome barriers to breastfeeding. There are many factors that influence one's decision to breastfeed and consequently influence weight trends. Utilizing national recommendations as a framework for the development of local programs can result in measurable public health improvements.

Conclusions:

This population-level analysis can help inform both national policies and recommendations on maternal health status, GWG, and infant feeding practices; and in turn transform obstetric, gynecology, and pediatric care. Carefully monitoring pre-pregnancy BMI, GWG, and promoting breastfeeding are three strategies that can lead to a decrease in rapid weight gain during infancy, reduce childhood obesity rates, and curtail the cycle of weight gain that is apparent across generations. Furthermore, the FDA and CDC are in the process of collecting follow-up data on the IFPS II cohort. This next wave of study data will lend itself to an analysis on GWG, infant feeding, and childhood obesity. Additional analyses should aim to assess feeding behaviors throughout infancy; including the timing of the introduction of solid foods and the nutritional quality of the solid foods. Incorporating nutrition data beyond infancy and into adolescence can further enhance our ability to understand the early antecedents of disease.

Interventions targeting upstream exposures; such as pre-pregnancy BMI, GWG, and infant feeding can influence growth trajectories and contribute to a shift in intergenerational population growth trends. National level data can be used to make state level comparisons, identify areas in need of attention, and develop local interventions to address the identified needs. The development of culturally sensitive programs that educate pregnant woman about maternal risks, and encourage healthy behaviors will enhance informed decision-making and can positively influence health outcomes. A focus on infancy is of equal importance. National recommendations are not always reflected in clinical practice. Breastfeeding promotion should be widely supported by healthcare providers as a childhood obesity prevention strategy. Furthermore, postpartum care is an important medical encounter for encouraging a healthy maternal weight and highlighting the benefits of breastfeeding for both mothers and infants. Clear, consistent messaging is critical to improving breastfeeding rates and intergenerational weight trends. Inclusion of a learning module on breastfeeding within medical training programs can ensure all health practitioners are made aware of the benefits of breastfeeding. Pre-pregnancy, pregnancy, and infancy appear to be critical points of opportunity during which small behavioral changes can lead to substantial public health benefit.

Appendices

Appendix A.1: Neonatal questionnaire excerpt:

In the past 7 days, how often was your baby fed each food listed below? Include feedings by everyone who feeds the baby and include snacks and night-time feedings. If your baby was fed the food once a day or more, write the number of feedings per day in the first column. If your baby was fed the food less than once a day, write the number of feedings per week in the second column. **Fill in only one column for each item.** If your baby was not fed the food at all during the past 7 days, write in 0 the second column.

	FEEDINGS PER DAY	**FEEDINGS PER WEEK**
Breast milk		
Formula		
Water		
Sugar Water		
Cow's milk or any other milk (rice, soy, goat, or other)		
100% fruit or 100% vegetable juice		
Sweet drinks (juice drinks, soft drinks, soda, sweet tea, Kool-Aid, etc.)		
Baby cereal		
Other (PLEASE SPECIFICY)		

Appendix A.2: Income categories questionnaire excerpt

Under $5,000	[ ]	$25,000 to $27,499	[ ]	$75,000 to $84,999	[ ]
$5,000 to $7,499	[ ]	$27,500 to $29,999	[ ]	$85,000 to $99,999	[ ]
$7,500 to $9,999	[ ]	$30,000 to $32,499	[ ]	$100,000 to $124,999	[ ]
$10,000 to $12,499	[ ]	$32,500 to $34,999	[ ]	$125,000 to $149,999	[ ]
$12,500 to $14,999	[ ]	$35,000 to $39,999	[ ]	$150,000 to $174,999	[ ]
$15,000 to $17,499	[ ]	$40,000 to $44,999	[ ]	$175,000 to $199,999	[ ]
$17,500 to $19,999	[ ]	$45,000 to $49,999	[ ]	$200,000 to $249,999	[ ]
$20,000 to $22,499	[ ]	$50,000 to $59,999	[ ]	$250,000 to $299,999	[ ]
$22,500 to $24,999	[ ]	$60,000 to $74,999	[ ]	$300,000 and over	[ ]

Appendix B: Calculating the difference in slopes

The following equations were used to estimate the difference in slopes before t* and after t*; where t* is a specific time point at which the slope for previous growth was compared with the slope for subsequent growth. This analysis assessed the change in infant growth from month three-month five versus month five-month twelve. The components of the equation are defined as follows:

E(Yij) = growth measures for the i^{th} subject at the j^{th} examination

βo=intercept

tij= is the observation time for subject i at the j^{th} examination

t*=change point

tij-t*= time minus change point

Xij-infant feeding type for the i^{th} subject at the j^{th} examination

Xijtij-the interaction of infant feeding and time

Xij (tij-t*)-the interaction of infant feeding and a change point

The following describes the equation before t* where tij represents a time point before t*:

|--------|
tij t*

In the following equation, $(tij\text{-}t^*)^+ = \{tij\text{-}t^* \text{ if } tij\text{-}t^* > 0;\ 0 \text{ if } tij \leq t^*\}$.

1A) $E(Yij) = \beta o + \beta 1tij + \beta 2(tij\text{-}t^*)^+ + \beta 3Xij + \beta 4Xijtij + \beta 5Xij\ (tij\text{-}t^*)^+ + bi$

In the time before t*, tij is less than t*. Therefore $(tij\text{-}t^*)^+ = 0$ so $\beta 2(tij\text{-}t^*)^+ = 0$ and $\beta 5Xij (tij\text{-}t^*)^+ = 0$ and can be dropped from the equation. The terms ahead of **tij** represent the slope:

1B) $E(Yij) = \beta o + \beta 1$**tij** $+ \beta 3Xij + \beta 4Xij$**tij** $+bi$

By rearranging the terms:

1C) $E(Yij) = \beta o + (\beta 1 + \beta 4Xij)$**tij** $+\beta 3Xij + bi$; where $\beta 1 + \beta 4Xij$ represents the slope before t* which depends on feeding type Xij).

Again, these terms can be rearranged as follows:

1D) $E(Yij) = \beta o + (\beta 1 + \beta 4Xij)$**tij** $+ \beta 3Xij + bi$

The slope before t* is $\beta 1 + \beta 4Xij$.

In the second equation, tij >t* since it represents a time point after t*:

|--------|

t*   tij

Note, in the first equation, before t*, $(tij - t^*)^+$ is equal to 0. But in the second equation tij is greater than t*, and therefore $(tij - t^*)^+ = tij\text{-}t^*$. The equation after t* can be written as follows. Note, each instance of $(tij - t^*)^+$ is now replaced with tij-t*:

2A) $E(Y_{ij}) = \beta_o + \beta_1 t_{ij} + \beta_2 (t_{ij} - t^*) + \beta_3 X_{ij} + \beta_4 X_{ij} t_{ij} + \beta_5 X_{ij} (t_{ij} - t^*) + b_i$

Which can be rewritten as follows. Note: The underlined text highlights the constants, which represent the intercept:

2B) $E(Y_{ij}) = \underline{\beta_o} + \beta_1 \mathbf{t_{ij}} + \beta_2 \mathbf{t_{ij}} - \underline{\beta_2 t^*} + \beta_3 X_{ij} + \beta_4 X_{ij} \mathbf{t_{ij}} + \beta_5 X_{ij} \mathbf{t_{ij}} - \underline{\beta_5 X_{ij} t^*} + b_i$

The model can be rewritten as follows:

2C) $E(Y_{ij}) = [\underline{\beta_o - \beta_2 t^* - \beta_5 X_{ij} t^*}] + [\beta_1 + \beta_2 + \beta_4 X_{ij} + \beta_5 X_{ij}] \mathbf{t_{ij}} + \beta_3 X_{ij} + b_i$

The slope after t^* is $\beta_1 + \beta_2 + \beta_4 X_{ij} + \beta_5 X_{ij}$. Finally, the difference in slopes:

(Slope before t^*) $\beta_1 + \beta_4 X_{ij}$

(Slope after t^*) $- \underline{\beta_1 + \beta_2 + \beta_4 X_{ij} + \beta_5 X_{ij}}$

$$= \; - (\beta_2 + \beta_5 X_{ij})$$

The difference in slopes is $- (\beta_2 + \beta_5 X_{ij})$ and is a function of infant feeding (X_{ij}).

Appendix C: Calculation of the difference in slopes for the month 5 change point

The values for the slope at the month five change point by feeding type were calculated using the following equation where:

βo= intercept

$\beta 1$ I (feed 1) = Mixed fed

$\beta 2$ I (feed 2)=Predominantly formula fed

$\beta 3t$=time

$\beta 4$ max$(t-2, 0)^{+}$= (time-t*) where t*=2

$\beta 5$ I (feed=1)t= Mixed fed *time

$\beta 6$ I (feed=2)t = Predominantly formula fed *time

$\beta 7$ I (feed=1) max (t-2,0) = Mixed fed by (time-t*)

$\beta 8$ I (feed=2) max (t-2,0)= Predominantly formula fed by (time-t*)

Note: Breastfeeding was the reference group.

$$Y = \beta o + \beta 1 \text{ I (feed 1)} + \beta 2 \text{ I (feed 2)} + \beta 3t + \beta 4 \max(t-2, 0) + \beta 5 \text{ I (feed=1)}t + \beta 6 \text{ I (feed=2)}t + \beta 7 \text{ I (feed=1)} \max(t-2,0) + \beta 8 \text{ I (feed=2)} \max(t-2,0)$$

Next, we must determine the equations for before and after the month five change point for each feeding type so that we can calculate the slopes.

Note: The slopes are underlined.

1A) **Mixed fed infants before** the month five change point:

$$Y = \beta o + \beta 1 + \underline{\beta 3}t + \underline{\beta 5}t$$

1B) **Mixed fed infants after** the month five change point:

$Y = \beta o + \beta 1 + \beta 3t + \beta 4(t\text{-}2) + \beta 5t + \beta 7(t\text{-}2)$

To isolate the slope we can rewrite this equation:

$Y = \beta o + \beta 1 - 2\beta 4 - 2\beta 7 + (\underline{\beta 3 + \beta 4 + \beta 5 + \beta 7})t$

Difference in slopes= $\beta 4 + \beta 7$

2A) **Formula fed infants before** the month five change point:

$Y = \beta o + \beta 2 + \underline{\beta 3}t + \underline{\beta 6}t$

2B) **Formula fed infants after** the month five change point

$Y = \beta o + \beta 2 + \beta 3t + \beta 4(t\text{-}2) + \beta 6t + \beta 8(t\text{-}2)$

Which simplifies to:

$Y = \beta o + \beta 2 + \beta 3t + \beta 4t - 2\beta 4 + \beta 6t + \beta 8t - 2\beta 8$

$Y = \beta o + \beta 2 - 2\beta 4 - 2\beta 8 + (\underline{\beta 3 + \beta 4 + \beta 6 + \beta 8})t$

Difference in slopes: $\beta 4 + \beta 8$

3A) **Breastfed infants before** the month five change point:

$Y = \beta o + \underline{\beta 3}t$

3B) **Breastfed infants after** the month five change point:

$Y = \beta o + \beta 3t + \beta 4(t\text{-}2)$

Which simplifies to:

$Y = \beta o - 2\beta 4 + (\underline{\beta 3 + \beta 4})t$

Difference in slopes: $\beta 4$

Appendix D: Estimates for the main effect and interaction of infant feeding and GWG

		Weight		Length		Weight-for-Length	
Main Effects		**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Infant Feeding	**Mixed**	0.42	(-0.02, 0.85)	0.04	(-0.30, 0.37)	0.02	(-0.01, 0.05)
	Formula	0.32	(0.00, 0.65)	-0.06	(-0.31, 0.19)	0.02	(-0.01, 0.04)
	Breastfed	--	--	--	--	--	--
GWG	**Inadequate**	-0.26	(-0.59, 0.07)	-0.39	(-0.64, -0.13)	0.00	(-0.03, 0.02)
	Excessive	0.19	(-0.05, 0.44)	-0.03	(-0.22, 0.15)	0.02	(0.00, 0.04)
	Adequate	--	--	--	--	--	--
Interactions	**Mixed*Inadequate**	0.55	(-0.17, 1.28)	0.79	(0.22, 1.36)	-0.01	(-0.06, 0.05)
	Mixed*Excessive	0.14	(-0.43, 0.70)	0.30	(-0.14, 0.73)	-0.02	(-0.06, 0.03)
	Mixed*Adequate	--	--	--	--	--	--
	Formula*Inadequate	-0.34	(-0.88, 0.20)	0.14	(-0.29, 0.57)	-0.01	(-0.06, 0.03)
	Formula*Excessive	0.26	(-0.16, 0.68)	0.23	(-0.10, 0.55)	0.00	(-0.02, 0.03)
	Formula*Adequate	--	--	--	--	--	--
	Breastfed*Inadequate	--	--	--	--	--	--
	Breastfed*Excessive	--	--	--	--	--	--
	Breastfed*Adequate	--	--	--	--	--	--

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