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Association Between Breastfeeding and Infant Growth: A Probable Reverse Causality

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ASSOCIATION BETWEEN BREASTFEEDING AND INFANT GROWTH: A PROBABLE REVERSE CAUSALITY

by

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ABSTRACT

Background: Much conflicting results exist in the association between breastfeeding and infant growth. One of these confusions is related to the temporal sequence between breastfeeding practice and infant growth.

Objective: This study aimed at examining the association and investigating a possible reverse causality between breastfeeding and infant growth.

Method: Infant Feeding Practices Survey II, a national longitudinal database with repeated measurements, following women prenatally and until one year postpartum (N=2914) was used. Mixed linear model assessed the impact of breastfeeding from the 2nd, 4th, 6th and 9th months on infant growth at the 3rd, 5th, 7th and 12th months, respectively. Log-linear model assessing reverse causation used infant growth data from the 3rd, 5th and 7th months and breastfeeding data from the 4th, 6th and 9th months respectively, restricting to infants' breastfed in the prior months or being exclusively breastfed in the first 5 months.

Results: Non-exclusively breastfed infants had a linear increase in mean weight-for-age z-score (WAZ) from the 3rd month (0.10) to the 7th month (0.34) while exclusively breastfed infants had a stable WAZ (0.27-0.24) (p-value for interaction=0.003). Non-breastfed infants had a higher WAZ throughout the first year (3rd month=0.20, 12th month=0.67) than infants who were ever breastfed in the first year (3rd month=0.04, 12th month=0.29) ($p<.0001$). Weight-for-length z-score (WLZ) showed similar results (p interaction=0.006). Log-linear model showed a 7% (95% Confidence Interval 1.00, 1.14) higher risk of continuing with exclusive breastfeeding with every unit increase in WAZ.

Conclusion: In earlier months WAZ was better in exclusively breastfed infants. Only WAZ showed some possibility of reverse causality suggesting weight gain as a predictor of continuation of exclusive breastfeeding.

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LIST OF ABBREVIATIONS

BF .... Breastfeeding

BMI .... Body Mass Index

CDC .... Centers for Disease Control and Prevention

DHHS... Department of Health and Human Services

EXBF .... Exclusive Breastfeeding

FDA .... Food and Drug Administration

ITT .... Intention to Treat

LAZ .... Length for Age z-scores

NIH .... National Institute of Health

PROBIT .... Promotion of Breastfeeding Intervention Trial

WAZ .... Weight for Age z-scores

WHO .... World Health Organization

WLZ .... Weight for Length z-scores

CHAPTER I

INTRODUCTION

Importance of Breastfeeding

Breastfeeding is considered to be an optimum source of nutrition for the first 6 months of infant life[1]. It is beneficial to both the mother and her infant. An infant's physical growth and cognitive development are improved through breastfeeding[2]. Breast milk protects an infant from various gastrointestinal, respiratory and other infections by providing antibodies and promoting development of his/her immune system[3-7]. In addition, breastfeeding helps to prevent obesity[8, 9] and cardiovascular diseases[10] in the later stages of life. Thus, it plays a vital role in reducing infant mortality by preventing infections and other diseases[11, 12]. Bonding between infant and mother improves with breastfeeding[13]. Post-partum weight loss is enhanced in women who breastfeed their infants[14]. Despite the numerous advantages of breastfeeding, breastfeeding proportions are not as expected, according to Healthy people 2020[15].

Breastfeeding and Infant growth

Some studies suggest that, from birth to 3 months, exclusively breastfed infants have similar or higher growth trajectories than non-exclusively breastfed infants[6, 7, 16]. After 3 months this difference decreases and in the later months the non-breastfed group show higher WAZ and WLZ.

Decisions regarding continuation of breastfeeding depend on various factors such as mothers' perception on breastfeeding, health status of infants and mother's perception regarding child's growth[5, 16-18]. Infant growth is one of the factors found to have an association with breastfeeding continuation; however there are debatable results regarding the impact of infant growth on breastfeeding. It has been shown that mothers who perceive that their infants are not growing as they should, have a higher probability of weaning their infants early[16, 17, 19]. A couple of studies have also shown that mothers with rapidly growing infants have a higher physical growth, so they need more energy that increases their demand for food[17, 20]Therefore mothers start with earlier weaning in these infants. These results show that infant growth can have an impact on breastfeeding decisions taken by mothers suggesting reverse causality. Given the inconsistent findings and the possible reverse causation in the association between breastfeeding and infant growth, it is essential to determine the direction of this association.

Purpose and Significance of the Study: All the above studies clearly show the dynamic nature of breastfeeding and infant growth relationship: Breastfeeding affects infant growth (original association) and infant growth affects breastfeeding continuation (reverse causation).By examining this relationship through the lens of reverse causality, we will gain an additional perspective that may shed light on the temporal sequence of early weaning decisions.

Our study is one of the first to investigate the possible reverse causal relationship between breastfeeding and infant growth using a US database, and will control for potential confounders involved in the weaning decision. The association will be assessed in both directions (breastfeeding to infant growth; infant growth to weaning) using delayed models. Our research question is to investigate probable reverse causality in the association between breastfeeding and infant growth. If there is reverse causation, we would observe that a slower infant growth precedes a mother's decision to wean her infant earlier. Also childhood obesity is on a rise in US. Breastfeeding is associated with infant weight gain and it is also supposed to impact childhood obesity[19]. Thus this decision and the processes related to it are especially important in light of the common belief that prolonged and exclusive breastfeeding slows a child's growth trajectory, thereby protecting against pediatric and childhood obesity.

Our research questions are as follows:

1) Does breastfeeding have an impact on infant growth (WAZ, LAZ and WLZ)?
2) Does infant growth have an effect on breastfeeding continuation for the infants who were breastfed (possible reversal causality)?

CHAPTER II

LITERATURE REVIEW

Breastfeeding: prevalence and problems with its association with infant growth

Our study aims to explore the temporal sequence between breastfeeding and infant growth. Thus the prevalence of breastfeeding is important to this study. If mothers do breastfeed, an understanding of the relationship between infant growth and breastfeeding may help mothers decide to exclusively breastfed longer, thereby granting more benefits to their infants.

Rates of breastfeeding have increased slightly but still falls short of the Healthy People (HP) 2020 goals[15]According to the 2011 CDC Immunization Survey, 74.6% of infants were breastfed at some point, 35% of U.S. infants were exclusively breastfed through 3 months of age, and 14% of infants were exclusively breastfed through 6 months of age, which were all below the HP 2020 goals, 81.9%, 46.2%, and 25.5%, respectively[15].

The relationship between infant growth and breastfeeding is an empirical relationship; it is therefore difficult to determine the exact temporal sequence and causality. Studies have been conducted to determine the impact of infant growth on breastfeeding practices, a reverse causality of the relationship between breastfeeding and infant growth. Some studies have evaluated factors which may lead to early weaning.

Proper data choice and correct analysis are essential for studies aimed at determining causal relationship.

Breastfeeding impacts infant growth

A detail review was conducted to specifically evaluate the benefits of breastfeeding and to determine the optimal duration of exclusive breastfeeding and continuation of any breastfeeding[19]. It concluded that breastfeeding influences infant health, and infant development and growth. Infants with complementary feeding and formula feeding have a higher growth as compared to breastfed infants in the later ages[16, 21-24].

However, the association varies by the intensity and timing of breastfeeding. Exclusively breastfed infants have a higher growth up to 3-4 months followed by similar growth when compared to formula fed infants[22]. From 6-12 months breastfed infants had a comparatively slower weight and length gain as compared to formula fed infants. A slightly different trend was seen in the randomized control trial conducted by Kramer and his associates[16]. Infant's weight was higher for exclusively breastfed group and it kept on increasing till 3rd month as compared to non-exclusively breastfed infants. Till the 12th month, no difference was detected between two groups. Another observational study conducted by Kramer et al. which was nested within the PROBIT[5] showed that infants who were exclusively breastfed up to 3 months followed by any breastfeeding until 6 months had a higher weight and length gain as compared to infants who were exclusively breastfed until 6 months. Not much difference could be seen during the 9-12 months. After stratifying the growth data based on feeding groups, Wright et al. found formula fed infants to be lighter at birth. Except birth, at all other time point's infant's breastfed for less than 6 weeks were heaviest and gained weight faster than infants who were breastfed for more than 4 months. Infants, who continued breastfeeding for the longest duration, had the smallest length after controlling for paternal height.

Echardt et al. examined the relationship between breastfeeding and infant growth from 0-6 months and 6-20 months in a Mexican community[24]. Weight was not significantly affected by the type of feeding from 0-6 months. Fully (either exclusively or pre-dominantly) breastfed infants for at least 4 months had ponderal index increment that was 0.07 units larger than children who were not. Infant who were fully breastfed for at least 4 months also had a significantly lower weight (-0.53 cm) and length (-0.72 kg) ponderal index increments than non-fully breastfed infants during age 6-20 months. They also tried to explore the potential impact of infant size on feeding choices made by mothers. An increase of 1 kg in lagged weight lead to higher odds of being fully breastfed at the age of 2 months. (OR=2.45, CI: 1.01-5.93).

Kalanda et al. conducted a cohort study in Malawian infants to compare the infant growth, morbidity incidence and risk factors for under nutrition among infants receiving early (before 3 months) complementary feeding and those who received it after 3 months[25]. Results showed that infants whose complementary feeding started within 3 months had lower weight for age at 3 months (p=0.02), 6 months (p=0.049) and 9 months (0.07) as compared to the other group.

All these studies showed that infants who were breastfed in the earlier months had a higher weight till 3-4 months as compared to non-breastfed infants. However, Morgan et al. used data from five prospective randomized trials in UK found different results. In their study, infants who were weaned before 3 months were heavier at 3 months as compared to infants weaned after 3 months (5.6 kg vs. 5.45 kg). Similar results were seen for length (59.04 cm vs. 58.56 cm). Infants weaned earlier showed a slower weight and length gain between 3-18 months as compared to infants weaned after 3 months. Both term and pre-term infants showed similar results[26].

Infant growth impacts breastfeeding

Although much is known about factors associated with early weaning, little has been published regarding the temporal sequence between infant growth and weaning. Li et al examined factors responsible for weaning during an infant's first year. This study utilized data obtained through the Infant Feeding Practices Study II (2005-2006). According to this study, factors were classified as lactational, psychosocial, nutritional, lifestyle, medical, milk-pumping, and infant self-weaning factors[18]. Infant's self-weaning and nutritional factors were found to be the leading reasons for early discontinuation of breastfeeding. "Breast milk alone did not satisfy my baby" and "I thought my baby was not gaining enough weight" were the leading nutritional causes for the discontinuation of breastfeeding across the 1-2, 3-5 and 6-8 months intervals. If a mother feels her child is not gaining the correct amount of weight for his/her age, she is more likely to begin introduction of foods that leads to early weaning. A meta-analysis of seven studies by Fewtrell et al. conducted in United Kingdom examined factors associated with an infant's age at weaning[27]. They found higher birth weight was significantly associated with early weaning (p-value=0.014) However weight at 6 weeks was a better predictor of early weaning after adjusting for birth weight and weight gain from birth to 6 weeks. Infants with heavier weight at 6 weeks were more likely to be weaned earlier. However, this study is a meta-analysis and mainly focused on gathering data on possible reasons for weaning. It did not address the temporal relationship between infant growth and age at weaning.

Wright et al. also undertook a UK-based study to determine factors associated with age of weaning[23]. This study used the data from the Millennium Baby Cohort Study, which prospectively collected data at 6 weeks, 4th, 8th and 12th months. Parents were also asked to maintain a weaning diary. The study found heavier babies to be weaned earlier than others, although weight gain over an interval was a better predictor of early weaning than a single weight measurement. Weight gain at 6 weeks was found to be most significant. However, this study's external validity is questionable. Breastfeeding proportions in the study population were lower than rates in the general population, as were breastfeeding initiation rates. In addition, age- and sex-specific anthropometric information was not included, making it difficult to assess the true association between infant growth and early weaning.

Two studies were conducted using the Promotion of Breastfeeding Intervention Trial (PROBIT) database shedding some light on the association between breastfeeding and infant growth[16, 17]. Kramer et al (2002) demonstrated that infants with lower weight and length gains tend to have prolonged and exclusive breastfeeding. According to the authors this could be due to reverse causality[16]. This study was conducted to examine the effects of selection bias and confounding possibly associated with infant growth and breastfeeding in a randomized control trial. The study employed two types of analytical techniques. Intention to treat (ITT) analysis using repeated measures regression model was done to assess the growth in the different randomized groups of breastfeeding. Logistic regression modeling was done for the observational data i.e. after ignoring the treatment groups (breastfeeding groups), combining the randomized group. Observational data analysis was specifically done to check for the probable reverse causation. The ITT analysis found a significant growth difference between breastfed and non-breastfed infants at 1 month; this difference increased at 3 months and thereafter and breastfed infants still had significantly higher weight gain when compared with other infants. Faster weight gain was associated with early weaning and those infants with slower weight gain were associated with delayed weaning according to the observational analysis. The sample size was large and they found a difference between the two groups, who were weaned earlier and other with prolonged exclusive breastfeeding with regards to the WAZ and LAZ scores. PROBIT, initially was not conducted with the main aim of assessing infant growth, therefore they did not standardize the height and weight measurements at different sites included in the trial. Thus generalization of results becomes difficult and this will lead to information bias.

Breastfeeding and Infant growth- reverse causation

Our study does not stand alone in the field; it aims to build upon and strengthen the knowledge gained from several prior studies which have examined reverse causation in the relationship between breastfeeding and infant growth.

Another study by Kramer et al. using PROBIT database focused on studying a potential reverse causality in the relationship between infant growth and breastfeeding[17]. Infants who were smaller at previous clinic visit were significantly more likely to have discontinued exclusive breastfeeding before their next clinic visit. In the bivariate analysis, as WAZ was a stronger predictor of breastfeeding decisions than LAZ, so multivariable analysis was only performed on the WAZ variable. The maximum effect was seen in the 2-6 month period; infants with a WAZ score <-1 had 20-60% higher odds of being weaned early when compared with other infants (OR=1.2-1.6). This study demonstrated reverse causality in the relationship between breastfeeding and infant growth. However, various confounders such as gastrointestinal infections and sleeping patterns were not adjusted for in the analysis. In addition, this study used data from the previously mentioned article by Kramer et al (2002) and therefore shared many of the same weaknesses such as non-standardization of all the growth measures across different study sites, cultural factors playing a role in determining the breastfeeding decisions etc.

Marquis et al. conducted a study in Peru to investigate causes of negative association between breastfeeding and infant size in children aged 12-15 months, as not many studies have been done in this age-group[28]. The median duration of breastfeeding for the study sample was 16.8 months. The association between weaning age and infant growth differed for children with low or high intake of complementary food... The study found that complementary food intake and diarrheal infection had an effect on feeding status of the infant at 14th months. With a high W/A in the 12th month, and increased diarrheal illness there was increased weaning in 14th month. Infants with poor health indicators were less likely to be weaned earlier. The decisions regarding weaning differed between the group of children with poor health and the group of children with high complementary food intake, high weight for their age and low diarrheal incidence. Weaning was measured at the end of 14th month; weight for age was measured at the 12th

months, complementary food intake at 9-11.9 months and diarrheal infection between 9-11.9 month and 12-14.9 months. Linear regression was used to examine the association between infant growth and weaning by using data collected at the same time period, controlling for other covariates. The delayed model was run using logistic regression to find the direction of association. They found diarrheal infection modified the association between weaning and infant growth. No overall association was detected between breastfeeding and infant growth until interaction terms between 9-11.9 month complementary food intake, 12 month weight-for-age and change in frequency of diarrheal infection between 9-15 months, were included in the model. After considering all the confounders and effect modifiers, it was seen that increased breastfeeding was associated with a decrease of 1 cm in length gain. With a decrease in weight-for age, there was a higher probability of continuing with breastfeeding, taking into account diarrheal morbidity and diet intake. The higher breastfeeding tendency may reflect cultural beliefs; hence it would be less likely to stop breastfeeding even if the baby is considered small. The breastfeeding tendency in this population was higher, thus mothers were less likely to discontinue with breastfeeding. The sample size was also small (n=134) and not representative of the entire Peruvian city. This affects the external validity of the study.

Summary

Studies on the impact of breastfeeding on infant growth show that breastfed infants have a higher weight and height till the first 3-4 months of infant's life. This difference is not very apparent in the later months of their life especially in the first year. Different types of study designs and analysis were used in all these studies. Some used ponderal index[25] as weight measurement, while others used weight gain[27] over a period of time or z-scores. Therefore it becomes difficult to compare results between different studies.

Studies on the factors associated with early weaning found infant size, especially infant weight, to be one of the main factors leading to early weaning. Studies found larger babies to be more likely to be weaned earlier[16, 23]. However, studies examining directionality such as Kramer et al. and Marquis et al. suggest that smaller infant size is associated with early weaning[17, 28]. Thus, all these studies did show an impact of infant growth on breastfeeding; however the trend in the association differed, based on WAZ i.e. some showed smaller size infants while some showed that rapidly growing infants were weaned earlier.

Methodological Issues in all these previous studies checking the associations in both the directions:

The data used for these studies were collected through cohort[23, 28] or randomized control trials[16, 17]. However longitudinal studies with repeated measurements should be done to specifically assess the association between infant growth and breastfeeding to determine the temporal sequence. Although in the above mentioned RCT, the sample size was large, it would be really difficult to select the participants. Also there may be ethical issues concerning the assignment of the intervention (breastfeeding) to selective participants. Bias could also lead to misclassifications and affect the associations found in the study. Z-scores of height and weight were used to measure infant growth by most of the studies, using WHO standards for this comparison. However the definition of breastfeeding and weaning was not specified consistently across the studies. In study conducted by Kalanda, they classified complementary feeding as inclusion of porridge-'phala' in the infant's diet[25]. Some studies included tea and broth under exclusive breastfeeding group. Studies using diet diaries recorded decrease in the number of replies over time[23, 28].

There are various other factors that could possibly act as confounders and are associated with early weaning. But the reviewed studies have not mentioned any specific ways to control for these factors. As seen from Fewtrell et al. study, diarrheal infection impacts infant weight and also breastfeeding decision, however other studies have not mentioned any specifics about these factors[27]. Delayed longitudinal models with repeated measurements would be a better study design for assessing temporal sequence including confounders into account.

CHAPTER III

METHODS

Infant Feeding Practices Survey II (IFPS II) Database

IFPS II was conducted in United States by the Food and Drug Administration (FDA) in collaboration with other health organizations, the Centers for Disease Control and Prevention, the Department for Health and Human Services , the National Institutes of Health and Maternal and Child Health Bureau in Health Services and Resource Administration. It is a longitudinal study with repeated measurements. The study was done with the main aim of understanding the need of improving health status of mothers and children. Data were collected from May 2005 through June 2007. The sample was selected from the Synovate consumer opinion panel. Number of pregnant women who volunteered to be a part of this study was around 4,900 at baseline. IFPS II used the following inclusion criteria for mothers to qualify for the study: being at least 18 years of age at the time of the prenatal questionnaire, having a stable address for at least 11 months, being proficient in English, being healthy and free of any serious long term health problem which would affect the feeding status. The inclusion criteria for infants to be followed were: being a full term or near to full term singleton birth, not staying in intensive care for more than 3 days, and no serious long term health problem and birth weight of at least 5 pounds. Participants were excluded from further mailing of questionnaires and follow-up of the post-natal questionnaire if their addresses were undeliverable, if they refused to participate, or if the questionnaires were not returned at either a single point of time or every time the questionnaire was administered. As a result, 2,971 women who had information on either infants feeding or infant growth measures for at least one time point beginning from 2nd month to the 12th month formed the basis for this study.

Birth screener, demographic, prenatal, neonatal and post-natal questionnaires were used to collect data. Except for the birth screener, all other data were collected through mailed questionnaires. Information about socio-demographic and infant feeding choices and early feeding practices was collected using the demographic, prenatal and neonatal questionnaires. Post-natal questionnaires were used to collect information regarding feeding status, health and growth of infants.

Definitions and Measures

<u>Infant Growth Measures</u>

Data on infant's height and weight were reported by their mothers in the 3rd, 5th, 7th and 12th months prospectively. As recommended by CDC, WHO standards were used to calculate age- and sex-specific z-scores[21, 29], that is, weight for length (WLZ), length for age (LAZ) and weight for age (WAZ) z-scores. Z-scores were used as a common footing for comparisons between age and gender and across the populations. For example, a Z-score represents the number of standard[22] deviation (SD) units above or below the mean. Unlike percentiles, a specified difference in Z-score represents the same difference in normalized BMI units for any age and both gender. In addition, because SD varies across ages, the same difference between 2 z-scores may represent a difference in

BMI units that is not constant across ages. Because of these advantages, we have chosen to use z-scores instead of percentiles and percent of medians[29, 30]. The use of WHO reference also makes our findings comparable with other studies as similar measures have been used in previous studies[17].

Feeding Measures

Feeding information was collected in all post-natal questionnaires. The question asked was "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 (per day)". The food items listed were as follows: breast milk, formula, cow's milk, other milk, other dairy foods, other soy foods, 100% fruit or vegetable juice, sweet drinks, baby cereal, other cereals, fruits, vegetables, French fries, meat, chicken etc., fish or shellfish, peanut butter, eggs, sweet foods and other. Using this information, breastfeeding status was categorized into exclusive breastfeeding and non-exclusive breastfeeding. Without any information on water intake in IFPS II, the exclusive breastfeeding variable was measured only on the basis of intake of food and other drinks, which is slightly different from the WHO standards of exclusive breastfeeding[1]. The other breastfeeding variable created was any breastfeeding and no breastfeeding. Any breastfeeding includes infants who have at least some amount of breastfeeding[29, 30].

Covariates

To examine the independent association between breastfeeding and infant's growth, other covariates were also considered in our models as potential confounders. They were socio-demographic factors (i.e., maternal race, income status and education), maternal factors (maternal pre-pregnancy body mass index, maternal height, smoking status), and infant's birth weight. Information about socio-demographic data came from demographic questionnaire, birth weight from the Birth Screener, and others coming from the prenatal questionnaire. As time is important while studying this association, month-time variable was included in analysis as a covariate. Month is the calculated categorical time variable specifically created for the delayed model showing the time of outcome measurement.

A difference was found between the age of infants at the return of questionnaires and the actual age of infant. Based on the available data, we used actual age of infants for correcting the breastfeeding and infant growth measures.

Statistical Methods and Analysis Plan

SAS 9.3 (SAS Institute Inc., Cary, NC, USA) was used for our analysis. Sample characteristics were presented for all participants who had at least one data point for breastfeeding or infant growth measures. We also presented the characteristics of the mothers at the 2nd month and the 3rd month, that provided data for our question 1 (to evaluate the association between breastfeeding and infant growth) and question 2 (to check the possible reverse causality between breastfeeding and infant growth), respectively. Descriptive statistics were calculated for breastfeeding and infant growth measures (anthropometric measurements-z scores) at different time points throughout the first year of the infant's life.

Delayed effect models were used for both the research questions (see Figures 3.1 and 3.2). Because delayed models use the independent variable at one time point to predict the dependent variable at subsequent time points, these models are useful to determine temporality of the association. The longitudinal data with repeated measurements can facilitate this type of modeling. In our study we used the delayed effect models to check directionality in this association and also to detect probable reverse causation between breastfeeding and infant growth.

To examine our research question 1, that is, the association between infant feeding and infant growth in the first year, we first conducted bivariate analysis using proc means. Significance of association was assessed using t-tests. Given that the outcomes of interests (WAZ, LAZ and WLZ) were continuous and measured repeatedly, the linear mixed model ("proc mixed") was used while conducting multivariable analysis. Crude and adjusted models were run separately for exclusive breastfeeding and any breastfeeding. Total subjects for the crude model was 2914, and for the adjusted model was 2380 due to additional missing values in the covariate adjusted. WHO recommends exclusive breastfeeding for the first six month[1], so we used the breastfeeding data from the 2nd, 4th, 6th months to predict its associations with infant growth measures (WAZ, LAZ and WLZ) in the subsequent months (the 3rd, 5th, and 7th month, respectively) (See Figure 3.1). Breastfeeding is recommended for the first 12 months of life for the infants, therefore breastfeeding data from the 2nd, 4th, 6th and 9th months were used to examine its association with the infant growth measures (WAZ, LAZ and WLZ) at the subsequent months (the 3rd, 5th, 7th and 12th month, respectively). Beta estimates and the respective p-values of the variables were presented.

For the 2nd research question on the effect of infant growth on breastfeeding (reversal causation), we first conducted a bivariate analysis to cross-tab categorical infant growth variables (i.e, z scores <-1, -1 to 1 and >1) and breastfeeding variables. Chi-square tests of independent were used (proc freq). The categorical infant growth variable was only used in the bivariate analysis and continuous infant growth measures were used in multivariable analyses. Log-linear model ("proc genmod") was used for the dichotomous outcome in repeated measurements. Similar to research question 1, we examined exclusive breastfeeding for up to 6 months only (i.e., the 4^{rd} and 6^{th} months) while the infant growth data were from the 3^{rd} and 5^{th} months respectively. Mothers who exclusively breastfed their infants at 3^{rd} and 5^{th} months respectively were selected for the analysis. Similarly infants who were breastfed at the 3^{rd}, 5^{th} and 7^{th} months were included in the analysis for any breastfeeding model. These models used the infant growth data from the 3^{rd}, 5^{th} and 7^{th} months to estimate the continuation of any breastfeeding at the 4^{th}, 6^{th}, and 9^{th} month, respectively (Figure 3.1). Risk ratio and its 95% confidence interval have been presented. In the log-linear model, for both (crude and adjusted) models the total number of observations read were n=3845, however the number of observations used for analysis varied across the three infant growth measures (WAZ, LAZ and WLZ) and two breastfeeding variables (exclusive breastfeeding and partial breastfeeding).

Proc Mixed and proc Genmod were selected over other methods of analysis as they are specially designed to handle for repeated data measurements on subjects over a period of time. Also we can we determine the best-fitting covariance matrix to compensate for within-subject correlations. Different covariance matrices were tested for mixed model as well as log-linear model (VC, CS, AR(1), TOEPLITZ, UN). The best covariance matrix (UN) was selected based on the Akaike Information Criterion (AIC), corrected AICC and Bayesian Information Criteria (BIC) values for proc mixed model QIC and QICu was used in the proc genmod model. Interaction terms were considered between month and feeding status in each model and significant ones were presented. In mixed models, least square means was used to check for the trend across the subcategories of the interaction terms. All the probable confounders were included in the model simultaneously in the initial model. Variables were checked for confounding effect using 10% rule. The full model consisted of maternal age, bmi, maternal height, educational status, race, parity, pre-pregnancy smoking status and infant birth weight. All the variables that were not confounders and had an insignificant p-value (>0.05) in both proc mixed and proc genmod models were removed from the models. Finally crude models were run with the main independent variable and outcome variable. Final (adjusted) models included the month, maternal race, parity and pre-pregnancy smoking status as categorical variables and maternal height and infant birth weight as continuous variables. Although IFPS II mentioned that low birth weight infants were excluded, around 1% of infants (n=54) had a low birth weight. A difference was not detected in the results after exclusion of the birth weight variable; therefore in our final analyses, we kept these 1% low birth weight babies in the models.

CHAPTER IV

MANUSCRIPT: ASSOCIATION BETWEEN BREASTFEEDING AND INFANT GROWTH: A PROBABLE REVERSAL CAUSALITY

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Abstract

The association between breastfeeding and infant growth show debatable results with regards to temporal sequence. The study aimed at examining the association between breastfeeding and infant growth and investigating the possible reverse causality in this association.

Data came from the Infant Feeding Practices Survey II, a national longitudinal database among women recruited prenatally and followed until one year of infants’ life from May 2005 through June 2007 (N =2914). Mixed linear model was used to assess the impact of breastfeeding from the 2nd, 4th, 6th and 9th months on infant growth (weight-for-age z-score (WAZ), length-for-age z-score (LAZ), and weight-for-length z-score (WLZ)) from the 3rd, 5th, 7th and 12th months. Reverse causation was evaluated with a log-linear model using infant growth data from the 3rd, 5th and 7th months and breastfeeding data from 4th, 6th and 9th months, restricting to infants breastfed in the 3rd, 5th and 7th months or those who were exclusively breastfed in the first 5 months.

Overall, there was an increase in mean WAZ (3rd month = 0.10 to 7th month = 0.34) among non-exclusively breastfed infants while exclusively breastfed infants had a stable WAZ (3rd month = 0.27 to 7th month = 0.24) (p for interaction = 0.003)). Non-breastfed infants had a higher WAZ throughout the first year (3rd month = 0.20, 12th month = 0.67) than infants who were ever breastfed in the first year (3rd month= 0.04, 12th month = 0.29) (p for interaction <.0001). Similar results were seen for WLZ (p for interaction = 0.006). Log-linear model showed that with one unit increase in WAZ the

chance of continuing exclusive breastfeeding was associated with a 7% (95% Confidence Interval 1.00, 1.14) higher risk of continuing with exclusive breastfeeding.

Our findings show that exclusively breastfed infants have a better WAZ in the earlier months. Some evidence of reversal causality was seen with WAZ and exclusive breastfeeding, but not LAZ and WLZ measures, suggesting weight gain to be a predictor of continuation of exclusive breastfeeding.

Introduction

Breastfeeding is beneficial for both infants and mothers that World Health Organization (WHO) recommends infant are exclusively breastfed for the first six months of life[1]. Yet the association between breastfeeding and infant growth is still inconclusive. Studies found that for the initial 3-4 months exclusively breastfed infants had a higher growth trajectory than non-exclusively breastfed infants[16, 21]. In the later infancy, breastfed infants have a relatively slower growth rate as compared to formula-fed infants[17, 23, 24]. This association between breastfeeding and infant growth could be due to probable reversal causality. Infant growth is one of the factors that play a role in weaning decisions taken by mothers. Studies have shown that mothers who perceive that their infants do not grow well as they should be, have a higher probability of weaning their infants early. To the opposite, mothers with rapidly growing infants perceive that their infants need more energy, as these infants may cry more demanding excess food and thus they start to wean the infants earlier. Controversies also exist in the association between breastfeeding and childhood obesity. Some studies suggest that rapidly growing infants are more likely to develop childhood obesity[9, 31]. From the studies mentioned previously, it can be implied that infants who are weaned earlier grow at a rapid pace and have a higher probability of developing childhood obesity. As infant growth is one of the factors responsible for decisions regarding weaning, therefore before decisions and policies are made with regards to breastfeeding and obesity, understanding of the directionality of this association is essential.

These diverse findings also show the dynamic nature of breastfeeding and infant growth relationship. By examining this relationship through the lens of reverse causality, we will gain an additional perspective that may shed light on the temporal sequence of early weaning decisions. Our study is one of the first to investigate the possible reverse causal relationship between breastfeeding and infant growth using a national database from the United States. We hypothesize that infant growth has an impact on a mother's decision to wean her infant earlier. This decision and the processes related to it are especially important in light of the common belief that prolonged and exclusive breastfeeding slows a child's growth trajectory, thereby protecting against pediatric obesity[17].

Our research questions are as follows:

1) Does breastfeeding have an impact on infant growth (Weight-for-age (WAZ)), (Length-for-age (LAZ) and (Weight-for-length (WLZ))?

2) Does infant growth have an effect on breastfeeding continuation for the infant (possible reversal causality)?

Data and Methods

Infant Feeding Practices Survey II (IFPS II) Database

IFPS II was conducted in United States by the Food and Drug Administration (FDA) in collaboration with other health organizations, the Centers for Disease Control and Prevention, the Department for Health and Human Services, the National Institutes of Health and Maternal and Child Health Bureau in Health Services and Resource Administration. It is a longitudinal study with repeated measurements. The study was done with the main aim of understanding the need of improving health status of mothers and children. Data were collected from May 2005 through June 2007. The sample was selected from the Synovate consumer opinion panel. Number of pregnant women who volunteered to be a part of this study was around 4,900 at baseline. IFPS II used the following inclusion criteria for mothers to qualify for the study: being at least 18 years of age at the time of the prenatal questionnaire, having a stable address for at least 11 months, being proficient in English, being healthy and free of any serious long term health problem which would affect the feeding status. The inclusion criteria for infants to be followed were: being a full term or near to full term singleton birth, not staying in intensive care for more than 3 days, and no serious long term health problem and birth weight of at least 5 pounds. Participants were excluded from further mailing of questionnaires and follow-up of the post-natal questionnaire if their addresses were undeliverable, if they refused to participate, or if the questionnaires were not returned at either a single point of time or every time the questionnaire was administered. 2,971 women had information on either infants feeding or infant growth measures for at least one time point beginning from 2nd month to the 12th month.

Birth screener, demographic, prenatal, neonatal and post-natal questionnaires were used to collect data. Except for the birth screener, all other data were collected through mailed questionnaires. Information about socio-demographic and infant feeding choices and early feeding practices was collected using the demographic, prenatal and neonatal questionnaires. Post-natal questionnaires were used to collect information regarding feeding status, health and growth of infants.

Definitions and Measures

Infant Growth Measures

Data on infant's height and weight were reported by their mothers in the 3rd, 5th, 7th and 12th months prospectively. As recommended by CDC, WHO standards were used to calculate age- and sex-specific z-scores[29], that is, weight for length (WLZ), length for age (LAZ) and weight for age (WAZ) z-scores. Z-scores were used as a common footing for comparisons between age and gender and across the populations. For example, a Z-score represents the number of standard deviation (SD) units above or below the mean. Unlike percentiles, a specified difference in Z-score represents the same difference in normalized BMI units for any age and both gender. In addition, because SD varies across ages, the same difference between 2 z-scores may represent a difference in BMI units that is not constant across ages. Because of these advantages, we have chosen to use z-scores instead of percentiles and percent of medians[29, 30]. The use of WHO reference also makes our findings comparable with other studies as similar measures have been used in previous studies[17].

Feeding Measures

Feeding information was collected in all post-natal questionnaires. The question asked was "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 (per day)". The food items listed were as follows: breast milk, formula, cow's milk, other milk, other dairy foods, other soy foods, 100% fruit or vegetable juice, sweet drinks, baby cereal, other cereals, fruits, vegetables, French fries, meat, chicken etc., fish or shellfish, peanut butter, eggs, sweet foods and other. Using this information, breastfeeding status was categorized into exclusive breastfeeding and non-exclusive breastfeeding. Without any information on water intake in IFPS II, the exclusive breastfeeding variable was measured only on the basis of intake of food and other drinks, which is slightly different from the WHO standards of exclusive breastfeeding[1]. The other breastfeeding variable created was any breastfeeding and no breastfeeding. Any breastfeeding includes infants who have at least some amount of breastfeeding[29, 30].

Covariates

To examine the independent association between breastfeeding and infant's growth, other covariates were also considered in our models as potential confounders. They were socio-demographic factors (i.e., maternal race, income status and education), maternal factors (maternal pre-pregnancy body mass index, maternal height, smoking status), and infant's birth weight. Information about socio-demographic data came from demographic questionnaire, birth weight from the Birth Screener, and others coming from the prenatal questionnaire. As time is important while studying this association, month-time variable was included in analysis as a covariate. Month is the calculated categorical time variable specifically created for the delayed model showing the time of outcome measurement.

A difference was found between the age of infants at the return of questionnaires and the actual age of infant. Based on the available data, we used actual age of infants when breastfeeding and infant growth measures were collected.

Statistical Methods and Analysis Plan

SAS 9.3 (SAS Institute Inc., Cary, NC, USA) was used for our analysis. Sample characteristics were presented for all participants who had at least one data point for breastfeeding or infant growth measures. We also presented the characteristics of the mothers at the 2nd month and the 3rd month, that provided data for our question 1 (to evaluate the association between breastfeeding and infant growth) and question 2 (to check the possible reverse causality between breastfeeding and infant growth), respectively. Percentages were calculated for categorical variables, while means were used for continuous variables. Descriptive statistics were calculated for breastfeeding and infant growth measures (anthropometric measurements-z scores) at different time points throughout the first year of the infant's life.

Delayed effect models were used for both the research questions (see Figures 3.1 and 3.2). Because delayed models use the independent variable at one time point to predict the dependent variable at subsequent time points, these models are useful to determine temporality of the association. The longitudinal data with repeated measurements can facilitate this type of modeling. In our study we used the delayed effect models to check directionality in this association and also to check for the probable reverse causation between breastfeeding and infant growth.

To examine our research question 1, that is, the association between infant feeding and infant growth in the first year, we first conducted bivariate analysis using proc means. Significance of association was assessed using t-tests. Given that the outcomes of interests (WAZ, LAZ and WLZ) were continuous and measured repeatedly, the linear mixed model ("Proc mixed") was used while conducting multivariable analysis. Crude and adjusted models were run separately for exclusive breastfeeding and any breastfeeding. Total subjects for the crude model was 2914, and for adjusted model was 2380 due to additional missing values in the covariate adjusted. WHO recommends exclusive breastfeeding for the first six month, so we used the breastfeeding data from the 2^{nd}, 4^{th}, 6^{th} months to predict its associations with infant growth measures (WAZ, LAZ and WLZ) in the subsequent months (the 3^{rd}, 5^{th}, and 7^{th} month, respectively) (See Figure 3.1). Breastfeeding is recommended for the first 12 months of life for the infants, therefore breastfeeding data from the 2^{nd}, 4^{th}, 6^{th} and 9^{th} months were used to examine its association with the infant growth measures (WAZ, LAZ and WLZ) at the subsequent months (the 3^{rd}, 5^{th}, 7^{th} and 12^{th} month, respectively). Beta estimates and the respective p-values of the variables were presented.

For the 2^{nd} research question on the effect of infant growth on breastfeeding (reversal causation), we first conducted a bivariate analysis to cross-tab categorical infant growth variables (i.e., z scores <-1, -1 to 1 and >1) and breastfeeding variables. Chi-square tests of independent were used (proc freq). The categorical infant growth variable was only used in the bivariate analysis and continuous infant growth measures were used in multivariable analyses. Log-linear model (“proc genmod”) was used for the dichotomous outcome in repeated measurements. Similar to research question 1, we examined exclusive breastfeeding for up to 6 months only (i.e., the 4rd and 6th months) while the infant growth data were from the 3rd and 5th months respectively. Mothers who exclusively breastfed their infants at 3rd and 5th months respectively were selected for the analysis. Similarly infants who were breastfed at the 3rd, 5th and 7th months were included in the analysis for any breastfeeding model. These models used the infant growth data from the 3rd, 5th and 7th months to estimate the continuation of any breastfeeding at the 4th, 6th, and 9th month, respectively (Figure 3.1). Risk ratio and its 95% confidence interval have been presented. In the log-linear model, for both (crude and adjusted) models the total number of observations read were n=3845, however the number of observations used for analysis varied across the three infant growth measures (WAZ, LAZ and WLZ) and two breastfeeding variables (exclusive breastfeeding and partial breastfeeding).

Proc Mixed and Proc Genmod were selected over other methods of analysis as they are specially designed to handle for repeated data measurements on subjects over a period of time. Also we can check for variance covariance matrices after considering for within subject correlations. Different covariance matrices were tested for mixed model as well as log-linear model (VC, CS, AR(1), TOEPLITZ, UN). The best covariance matrix (UN) was selected based on the Akaike Information Criterion (AIC), corrected AICC and Bayesian Information Criteria (BIC) values. Interaction was checked between month and feeding status in each model and significant ones were presented in Figures. Least square means was used to check for the trend across the subcategories of the interaction terms.

All the probable confounders were included in the model simultaneously in the initial model. Variables were checked for cofounding effect using 10% rule. The full model consisted of maternal age, bmi, maternal height, educational status, race, parity, pre-pregnancy smoking status and infant birth weight. All the variables that were not confounders and had an insignificant p-value (>0.05) in both proc mixed and proc genmod models were removed from the models. To remove information bias, insignificant covariates in only one of the models were not excluded. Finally crude models were run with the main independent variable and outcome variable. Final (adjusted) models included the month, maternal race, parity and pre-pregnancy smoking status as categorical variables and maternal height and infant birth weight as continuous variables. Although IFPS II mentioned that low birth weight infants were excluded, around 1% of infants (n=54) were low birth weight babies at the beginning time points for the two statistical models. A difference was not detected in the results after exclusion of the birth weight variable; therefore in our final analyses, we kept these 1% low birth weight babies in the models.

Results

Study population: In IFS II 2,971 participants had data on either breastfeeding or infant growth at any time point during the 1st year. As shown in Table 1, three out of five of these mothers were aged between 18 and 29 years old. Forty-five percent of these mothers were normal weight (body mass index (BMI) n=1329), half of them being overweight or obese (BMI≥25), and 5% were underweight (BMI < 18.5). A majority of these mothers were non-Hispanic whites (84.6%), had more than high school education

(80%), were parous at the interview time (70%), and did not smoke before pregnancy (90%). The mean birth weight for their infants was 3.45 kg.

Table 4.1 also presents the sample characteristics for 2784 mothers who had data for the 2nd month breastfeeding or 3rd month infant growth data. This sample offered information on the mothers who will be included for our proc mixed model. The 3rd month sample in Table 1 gave information of the beginning month for our log linear model used in research question 2. These samples were restricted to infants who were exclusively breastfed or had any breastfeeding in the 3rd month. After considering missing values in growth measures at 3rd months and missing values in exclusive or any breastfeeding variables from the 4th month, our sample sizes was 859 for exclusive breastfeeding model and 1416 for any breastfeeding model. When comparing across the samples, the sample characteristics were similar except that over 90% being married among those who responded to the 2nd month questionnaire.

Association between breastfeeding status and infant growth: Table 4.2 presents the mean infant growth measures at the 3rd, 5th, 7th, and 12th months by infant's breastfeeding status in the prior month, respectively. The mean WAZ at the 3rd month was significantly higher in infants who were exclusively breastfed in the 2nd month than non-exclusively breastfed infants (0.06 vs. -0.06, $p< 0.05$). The means at the 7th month were also significantly higher among infants who were exclusively breastfed at the 6th month compared to those who were not exclusively breastfed (0.39 vs. -0.14, $p<0.01$). For WLZ, we observed an opposite trend (-0.15 for exclusively breastfed infants and 0.37 for non-exclusively breastfed infants, $p<0.01$).

The mean WAZ at the 7th and 12th month among infants with any amount of breastfeeding was significantly lower than infants who were not breastfed in the previous 6th month (-0.01 vs. 0.34, p<0.001) and 9th (0.09 vs. 0.53, p<0.001) months, respectively. Similar pattern was observed for WLZ measure. The mean WLZ at the 5th, 7th, 12th month among infants who were breastfed for any amount at the 4th, 6th, and 9th months were significantly lower than infants who were not breastfed in those months. No difference was found with LAZ by any amount of breastfeeding within the 1st year.

We further evaluated the association between breastfeeding (exclusive and any) with infant growth measures using delayed models. Crude delayed model (n=2895) showed that exclusive breastfeeding in the first 6 months did not have a significant impact on average WAZ score. After adjusting for month, maternal height, infant birth weight, maternal race, parity, pre-pregnancy smoking status, and the interaction term between month and breastfeeding, exclusive breastfeeding in the first 6 months was significantly associated with an increase in WAZ score (p-value=0.0002) (Table 4a). Due to the significant interaction term between month of feeding and exclusive breastfeeding, we presented the mean WAZ score at the 3rd, 5th, and 7th month by breastfeeding status. Mean WAZ increased from the 3rd month (0.095), to the 5th month (0.1708), to the 7th month (β =0.3366) for non-exclusively breastfed infants. Over the same period, WAZ score was very stable for infants who were exclusively breastfed (See Figure 4.1). Infant's birth weight and maternal height were significantly associated with WAZ score. In delayed model, WLZ and LAZ were not significantly affected by breastfeeding status of infants.

The crude delayed model (Table 3b) showed us that any breastfeeding had a significant impact on WAZ and WLZ scores in first 12 months, WAZ (β =-0.25, p-value<0.0001) and WLZ (β= -0.49, p-value<.0001) while LAZ was insignificant in both crude (β =0.1147, p-value=0.0727) and adjusted (β=-0.0854, p-value=0.2030) models. Due to the significant interaction term any breastfeeding group and month the WAZ and WLZ score was presented at the 3^{rd}, 5^{th} 7^{th} and 12^{th} months in the two groups (any breastfeeding/ no breastfeeding) The number of subjects in the model with any breastfeeding had (N=2914) in crude and (N= 2380) in adjusted models. Observations used for analysis included (N= 5252) for WAZ, (N=3686) for LAZ and (N=3549) for WLZ. Among non-breastfed infants the WAZ score increased from 3^{rd} month (0.1447) to 5^{th} month (0.2432), to 7^{th} month (0.5072) to the 12^{th} month (0.7194), while for any breastfeeding group it remains stable 3^{rd} month (0.1282) to 12^{th} month (0.2081) after decreasing initially for 5^{th} month (0.0617) and 7^{th} month (0.0917) (See Figure 4.2). Among the non-breastfed group, WLZ followed a similar pattern i.e. from 3^{rd} month (0.4442) to 5^{th} month (0.6476) to 7^{th} month (0.6476) to the 12^{th} month (β =1.4707). Unlike WAZ, WLZ among any breastfed group increased over the same period from 0.3630 in 3^{rd} month to 0.7773 in the 12^{th} month (See Figure 4.3). Overall non-breastfed infants had a higher WAZ and WLZ throughout the as compared to any-breastfed infants throughout the time period. Infant birth weight, maternal race had a significant association with both WAZ and WLZ scores. Among the other covariates maternal height was significantly associated WAZ and maternal prenatal smoking status was significantly associated with WLZ (Table 3b).

Association between infant growth and breastfeeding practices- reverse causality: For Crude and Adjusted models, total number of observations read (N=1422). As a result of the restriction and availability of data regarding different variables, analysis was carried out on (N=876) for WAZ, (N=682) for LAZ, (N=653) for WLZ. In the models (table 5) only WAZ had a slight significant impact on exclusive breastfeeding status of the infant in both crude (Risk Ratio=1.04, CI (1.01, 1.09)) and adjusted (Risk Ratio=1.07, CI (1.003, 1.14) models. As seen from the crude results; for every unit increase in WAZ score the chances of being exclusively breastfed was increased by 1.04. LAZ score also shows a significant effect on exclusive breastfeeding status only in crude model. In the adjusted model the chances of being exclusively breastfed are 6% higher for every unit increase in WAZ. For every unit increase in LAZ score, the chances of being exclusive breastfed multiply 1.053 times. However after adjusting for other factors LAZ score became insignificant.

After adjusting (table 6a, table 6b) for other factors (month, maternal height, infant birth weight, maternal race, parity, pre-pregnancy smoking status), only WAZ has a significant impact on exclusive breastfeeding status of infant in the next visits. The other variables that were significant in the adjusted model for WAZ were month and maternal height. For every inch increase in maternal height, the chances of being exclusively breastfed decreases by 0.979 units. As compared to month4, there was a decrease in the chances of being exclusively breastfed at month6 (RR=0.329, CI (0.272, 0.399)). None of the other variables had a significant impact on the breastfeeding status of the infants in the next visits. Both LAZ and WLZ had no impact on exclusive breastfeeding status of infant in the adjusted models. WAZ, LAZ and WLZ also did not have any significant effect on any breastfeeding status of infants.

Means of the infant growth measures (WAZ, LAZ and WLZ), at the 3rd, 5th, 7th and 12th months and percentages of infants who were either exclusively breastfed or who had any breastfeeding at different time points can be seen in table 4.7. Frequency of exclusively breastfed infants decreases steadily from 2nd month (39%) to 5th month (22.38%), after which it drastically reduces in the 6th month (6.75%). After the 2nd month, for the infants who had any breastfeeding, the percentages decreases gradually from the 2nd month (68.98%) to 9th month (45.68%), followed by month 12th with 25.87% having any amount of breastfeeding. In the second month (i.e. at the beginning time point of the post-natal questionnaire) 39% (1051/2695) of mothers exclusively breastfeed their infants.

Discussions

One of the important findings in this study was that with the increase in the number of months, the infants who were exclusively breastfed had a higher weight until the 3rd month as compared to non-exclusively breastfed infants. This finding is consistent with prior studies by Nommsen Rivers and Dewey[21, 22]. At 5th month, the mean WAZ was not different among exclusively and non-exclusively breastfed infants. From month 5 to 7, non-exclusively breastfed infants had higher WAZ than exclusively breastfed infants. We also found that infants who did not have any breastfeeding at any time during the first 12 months had a higher weight during the 1st year than infants who had at least some breastfeeding. As seen in the results, infants who were not exclusively breastfed till 6 months or were not breastfed throughout the 1st 12 months had a continuous increase in weight with an increase in time. Furthermore, we also found evidence (Risk ratio= 1.07) of reverse causality in the association between breastfeeding and infant growth. That is, with the increase in the weight-for-age Z score, the chances of being exclusively breastfed at next visit increases modestly and significantly.

The association between breastfeeding and infant growth was consistent with the results from previous studies by Dewey et al.[21] and Kramer et al[16]. Exclusive breastfeeding determines the infant growth till 3 to 4 months. Exclusively breastfed infants have a higher weight than non-exclusively breastfed infants up till 3-4 months. After 4th month non-exclusively breastfed infants have a higher weight (WAZ and WLZ) than exclusively breastfed infants as seen in Dewey et al study. Unlike other studies, in our study we could not find any impact of breastfeeding on length of infants.

Previous studies reported different results in checking reverse causation. As discussed earlier, Marqius et al.[28] found that infants with slower growth have a higher probability of continuation of breastfeeding. In contrast to this study, our study showed that increase in weight leads to a higher chance of being exclusively breastfed in the subsequent visits. This is consistent with findings by Kramer et al[17]. While checking for confounders in this association, it was seen that the month of feeding and maternal height had an impact of breastfeeding. With an increase in the months there was a decrease in continuation of exclusive breastfeeding.

Besides the main association between breastfeeding and infant growth measures, infant birth weight (kg), maternal height (inches), and pre-pregnancy smoking also were associated with the weight of the infant. Increase in infant's birth weight and maternal height lead to an increase in weight of the infants on average. Overall results also showed that compared to non-Hispanic whites, non-Hispanic blacks had infants with higher weight. Studies have also shown that mothers who smoke during pregnancy have infants with higher BMI, and weight[32, 33]. In this study we found that mothers who smoked before pregnancy also had infants with higher weight.

Inclusion of covariates was based on the previous study results and significance of variables in these models. Besides parity, pre-pregnancy smoking, maternal race, height, birth weight and month other covariates were also included in the models, however only the above mentioned variables were significant in at least one of the models. Although maternal age and body mass index have shown some significance in the some of the previous studies, it was not significant in this study in either of the models and therefore they were excluded from the model.

WHO's definition[30] on breastfeeding status was used so that our findings can be comparable to other published studies[17]. Infant growth measures were measured at 4 time points and WAZ, LAZ and WLZ were calculated using the WHO-I-grow-up statistical package to avoid any biases and to maintain the comparability of our findings with prior studies. One possible limitation with breastfeeding measure is that IFS II asked mothers to report the infant's breastfeeding status in the past 7 days prior to the interview. Thus, using this one week breastfeeding status to represent the whole month would be either underestimate or overestimate the effects of breastfeeding depending on whether the 7 days fall in which portion of the month. It would have been beneficial if the data regarding feeding was collected for the entire month or at least 15 days.

To detect temporality, we intentionally used the exposure from the prior time interval to predict the outcome in the subsequent time interval. Delayed models were employed to investigate the directionality in the association between breastfeeding and infant growth. While detecting breastfeeding effect on infant growth, we used the 2nd, 4th, 6th, and 9th months breastfeeding data and 3rd, 5th, 7th and 12th month infant growth data respectively similarly. To assess reverse causation, we used the 3rd, 5th and 7th months growth measures and 4th, 6th and 9th months breastfeeding data respectively. Therefore, in our study either the breastfeeding information or infant growth measures preceded each other. As exclusive breastfeeding is recommended till 6th months, data analysis for exclusive breastfeeding was done using the data till 6th month while any breastfeeding analysis was conducted using the 6th and 12th month data. In order to check for the shift of infants from exclusive breastfeeding to non-exclusive breastfeeding and any breastfeeding to no breastfeeding for reverse causation both the models were restricted to exclusive breastfeeding and any breastfeeding groups in the previous months. One of the advantages of the study was that the data were repeatedly collected at 4 time points. The method used for analysis in repeated measurements here, reduces the within-subject variation as infants serve as their own control. Previous studies by Eckhardt et al and Marquis et al have used linear regression[24, 28]and survival analysis, respectively for studying factors associated with breastfeeding and assessing reverse causality. . One of the best ways to analyze a longitudinal data with repeated measurements is by using proc mixed and proc genmod. As these methods handle for missing data and do not require the same number of observations per subject, it was very useful in this study.

This is one of the very few studies done specifically in US to determine reverse causation in the association between breastfeeding and infant growth. Although the database is from entire US, the sample is not nationally representative. The mothers selected for the study were of higher socio-economic class and most of the mothers were Non-Hispanic Whites. The sample size estimating the breastfeeding impact on infant growth is larger as compared to the reversal causality. Although the weight and height measurements were taken in doctor's clinics, all the data were reported by mothers. This may lead to information bias.

Conclusion

In brief, our study found that non-exclusively breastfed infants show a higher weight after 3rd month and, after this time, non-breastfed infants show a higher weight throughout the infant's first year as compared to any breastfed infants. We also found that higher weight infants are more likely to continue with exclusive breastfeeding in the subsequent visit, which is supportive of our research question 2. Mothers of infants who have a slower growth trajectory may feel that breast milk is not sufficient enough for their infants and tend to start with other items of food besides breast milk. Mothers of infants with a rapid growth trajectory feel that the infant is growing at a good rate and so continue with exclusive breastfeeding. However from this study we can determine that infant weight at different time points had an impact on exclusive breastfeeding continuation in the follow-up visit on an average for first 6 months of infant life.

After detecting the expected impact of breastfeeding on infant growth, we also found that even infant growth plays a role in continuation of breastfeeding by mothers.

Certain factors that could be probable signs of hunger like crying could not be included in our study due to unavailability of data. Similar factors can be included in further studies. This study proves reverse causation and can help further studies elucidating this association and studies determining the association between obesity and infant growth.

Table 4.1: Sample characteristics of study participants

		Beginning time points for both models		
SAMPLE CHARACTERISTICS	At any time point	Month2 (exclusive/any breastfeeding) (for model 1)	month3 with exclusive breastfeeding (for model2)	month3 with any breastfeeding (for model2)
Total	(N=2971) % (n)	(N=2784) % (n)	(N=859) % (n)	(N=1416) % (n)
Mother's Age				
18-25	29.46 (807)	28.87 (743)	19.37 (154)	21.35 (281)
26-29	29.86 (818)	30.03 (773)	33.58 (267)	32.37 (426)
30-34	23.80 (652)	23.93 (616)	27.55 (219)	26.37 (347)
>34	16.87 (462)	17.17 (442)	19.5 (155)	19.91 (262)
Missing	(232)	(210)	(64)	(100)
Maternal Pre-pregnancy Body Mass Index				
Underweight	4.60 (135)	4.62 (127)	4.58 (39)	3.99 (56)
Normal	45.30 (1329)	44.91 (1235)	50.94 (434)	48.93 (687)
Overweight	26.31 (772)	26.18 (720)	24.77 (211)	25.43 (357)
Obese	23.79 (698)	24.29 (668)	19.72 (168)	21.65 (304)
Missing	(37)	(34)	(7)	(12)
Mother's Race				
Non_hisp_white	84.63 (2445)	84.94 (2306)	90.13 (758)	86.20 (1193)
Non_hisp_black	4.67 (135)	4.57 (124)	2.02 (17)	3.40 (47)
Hispanic	6.16 (178)	5.89 (160)	3.69 (31)	5.64 (78)
Other	4.53 (131)	4.60 (125)	4.16 (35)	4.77 (66)
Missing	(82)	(69)	(18)	(32)
Maternal Education				
<High school	20.81 (569)	20.50 (528)	11.86 (99)	13.42 (183)
High school/ College	40.16 (1098)	40.06 (1032)	33.05 (276)	36.07 (492)
College/Graduate/Post-grad	39.03 (1067)	39.44 (1016)	55.09 (460)	50.51 (689)
Missing	(237)	(208)	(24)	(52)

Table 4.1: Continued. Sample characteristics of the participants

SAMPLE CHARACTERISTICS	At any time point	Month2 (exclusive/any breastfeeding) (for model 1)	month3 with exclusive breastfeeding (for model2)	month3 with any breastfeeding (for model2)
Total	(N=2971) % (n)	(N=2784) % (n)	(N=859) % (n)	(N=1416) % (n)
Infant Birthweight				
Low birth weight	1.82 (54)	1.51 (42)	0.47 (4)	0.99 (14)
Normal	86.77 (2578)	87.14 (2426)	86.38 (742)	87.43 (1238)
High birth weight	11.41 (339)	11.35 (316)	13.15 (113)	11.58 (164)
Parity				
Primiparous	29.07 (842)	29.19 (794)	23.36 (199)	25.30(354)
Multiparous	70.93 (2054)	70.81 (1926)	76.64 (653)	74.70 (1045)
Missing	(75)	(64)	(7)	(17)
Pre-pregnancy Smoking Status				
No	90.07 (2666)	90.23 (2503)	97.78 (838)	96.18 (1359)
Yes	9.93 (294)	9.77 (271)	2.22 (19)	3.82 (54)
Missing	(11)	(10)	(2)	(3)
Mother's Marital Status				
Married	79.35 (2183)	79.51 (2061)	90.57 (759)	86.77 (1187)
Unmarried	20.65 (568)	20.49 (531)	9.43 (79)	13.23 (181)
Missing	(220)	(192)	(21)	(48)
	Mean (N)	Mean (N)	Mean (N)	Mean (N)
Infant Birth Weight (kgs)	3.454 (2971)	3.456 (2784)	3.5 (859)	3.48 (1416)
Maternal Height (inches)	65.10 (2966)	65.10 (2779)	65.24 (857)	65.11 (1414)

Table 4.2: Bivariate analysis of mean infant growth at different timepoints by infant's breastfeeding status in the respective previous month using t-test

	3rd			5th			7th			12th		
	WAZ	LAZ	WLZ	WAZ	LAZ	WLZ	WAZ	LAZ	WLZ	WAZ	LAZ	WLZ
	(N) Mean	(N) Mean	(N) Mean	(N) Mean	(N) Mean	(N) Mean	(N) Mean	(N) Mean	(N) Mean	(N) Mean	(N) Mean	(N) Mean
Exclusive Breastfeeding	*							**	**			
NO	(983) -0.06	(749) 0.06	(683) -0.03	(1024) -0.02	(710) -0.005	(689) 0.11	(1395) 0.18	(741) -0.14	(726) 0.37	-	-	-
YES	(757) 0.06	(613) 0.17	(570) -0.04	(499) 0.003	(375) 0.09	(364) -0.07	(110) 0.02	(63) 0.39	(63) -0.15	-	-	-
Any Breastfeeding						**	***		***	***		***
NO	(493) -0.066	(371) 0.019	(335) 0.06	(617) 0.061	(419) 0.039	(415) 0. 271	(731) 0.336	(372) -0.101	(364) 0.625	(717) 0.526	(539) -0.19	(533) 1.053
YES	(1247) 0.019	(991) 0.141	(918) -0.071	(906) -0.058	(666) -0.021	(638) -0.095	(664) -0.011	(369) -0.092	(362) 0.072	(692) 0.093	(535) 0.084	(524) 0.334

*p-value<0.05, **p-value<0.01,
***p- value<0.001
WAZ- weight for age z-score, LAZ- length for age z-score,
WLZ- weight for length z-score

Table 4.3a: β estimates in the delayed model using repeated measurement with exclusive breastfeeding in crude and adjusted models.

(Total no. of subjects=N) (observations used = n)	Weight-for-Age Z-score		Length-for-Age Z-score		Weight-for-Length Z-score	
	(β)	p-value	(β)	p-value	(β)	p-value
Exclusive Breastfeeding (Crude) (N=2895)	n=4768 0.0511	0.153	n=3251 0.162	0.0247	n=3095 -0.1621	0.1263
Exclusive Breastfeeding (Adjusted) (N=2368)	n=4048 0.1734	0.0002	n=2767 0.0122	0.8706	n=2644 0.0232	0.7834
Month						
7	0.2412	<.0001	-0.2511	0.021	0.4332	<.0001
5	0.0753	0.0483	-0.0785	0.249	0.1001	0.167
3	0		0		0	
Month*Exclusive breastfeeding			N/S	N/S	N/S	N/S
Exclusive breastfeeding_month7	-0.2686	0.0242				
Exclusive breastfeeding_month5	-0.1698	0.0065				
Exclusive breastfeeding_month3	0					
Maternal Height (inches)	0.0397	<.0001	0.0818	<.0001	-0.0203	0.2056
Infant birth weight (kgs)	0.9854	<.0001	1.1974	<.0001	0.1866	0.0541
Race						
Non-hispanic black	0.3913	0.0016	-0.2948	0.164	0.9112	0.0002
Hispanics	0.1656	0.1094	-0.09	0.6136	0.325	0.1046
Other	0.0795	0.4872	-0.3024	0.1086	0.203	0.3557
Non-hispanic White (Ref)	0		0		0	
Parity						
Multiparous	-0.0612	0.2256	-0.1473	0.0702	0.1399	0.1347
Nulliparous (ref)	0		0		0	
Pre-pregnancy Smoking						
Yes	0.0788	0.36	-0.04987	0.7332	0.4186	0.0135
No (ref)	0		0		0	

All the adjusted models are adjusted for month, maternal height, birth weight, maternal race, parity, pre-pregnancy smoking status. N/S – not significant

Table 4.3b: β estimates in the delayed model using repeated measurement with any breastfeeding in crude and adjusted models

(Total no. of subjects=N) (observations used =n)	Weight-for-age z-scores (β)	p-value	Length-for-Age z-scores (β)	p-value	Weight-for-Length z-scores (β)	p-value
Any breastfeeding (Crude) (N=2914)	n=6177 -0.2524	<.0001	n=4325 0.0977	0.167	n=4125 -0.4917	<.0001
Any breastfeeding (Adjusted) (N=2380)	n=5252 -0.0165	0.7619	n=3686 -0.0843	0.2585	n=3549 -0.0811	0.5275
Month						
12	0.5748	<.0001	-0.3053	0.0003	1.0266	<.0001
7	0.3625	<.0001	-0.2994	0.0043	0.6735	<.0001
5	0.09852	0.0591	-0.0963	0.1563	0.2035	0.1288
3	0		0		0	
Any breastfeeding*Month						
Any breastfeeding *month12	-0.4948	<.0001	N/S	N/S	-0.6122	0.0013
Any breastfeeding *month7	-0.399	<.0001			-0.4652	0.0127
Any breastfeeding *month5	-0.1649	0.0098			-0.1826	0.2567
Any breastfeeding *month3	0				0	
Maternal Height (inches)	0.043	<.0001	0.0882	<.0001	-0.0192	0.1917
Infant birth weight (kgs)	0.9081	<.0001	1.1472	<.0001	0.2338	0.008
Race						
Non-hispanic black	0.3324	0.004	-0.3741	0.0698	1.0248	<.0001
Hispanics	0.1951	0.0399	-0.1179	0.4888	0.3376	0.0621
Other	0.0145	0.8911	-0.273	0.133	0.0355	0.8578
Non-hispanic White (Ref)	0		0		0	
Parity						
Multiparous	-0.067	0.1505	-0.1969	0.0126	0.1523	0.0735
Nulliparous (ref)	0		0		0	
Prenatal Smoking						
Yes	0.0228	0.7759	-0.1236	0.3893	0.3963	0.0118
No (Ref)	0		0		0	

All the adjusted models are adjusted for month, maternal height, birth weight, maternal race, parity, pre-pregnancy smoking status. N/S- not significant

Table 4.4: Bivariate analysis: Infants-discontinuing with exclusive and any breastfeeding in the next visit with Infant growth measures (WAZ, LAZ and WLZ) in the previous visit

Growth Measures	% Who discontinued exclusive breastfeeding		% Of infants who discontinued breastfeeding		
	4th month	6th month	4th	6th	9th
	% (N)	% (N)	% (N)	% (N)	% (N)
WAZ (TOTAL)	25.17 (596)	75.59 (381)	6.50 (938)	11.34 (917)	3.18 (787)
<-1	28.36 (67)	76.19 (63)	10.00 (130)	14.09 (149)	1.59 (126)
-1 to 1	25.36 (414)	77.39 (261)	6.44 (652)	10.82 (619)	3.66 (519)
>1	22.61 (115)	66.67 (57)	3.85 (156)	10.74 (149)	2.82 (142)
LAZ (TOTAL)	24.69 (486)	74.73 (277)	7.12 (758)	11.06 (678)	2.73 (440)
<-1	23.08 (91)	75 (56)	6.08 (148)	12.58 (151)	2.15 (93)
-1 to 1	28.03 (239)	78.71 (155)	8.36 (383)	10.22 (362)	2.73 (220)
>1	20.51 (156)	65.15 (66)	5.73 (227)	11.52 (165)	3.15 (127)
WLZ					
Total	24.67 (458)	74.07 (270)	7.11 (703)	11.21 (651)	2.75 (436)
<-1	28.7 (108)	73.85 (65)	6.43 (171)	14.08 (142)	1.94 (103)
-1 to 1	23.83 (256)	73.08 (156)	7.55 (384)	10.75 (372)	3.20 (219)
>1	22.34 (94)	77.55 (49)	6.76 (148)	9.49 (137)	2.63 (114)

WAZ- Weight-for-age z-scores
LAZ- Length-for-age z-scores
WLZ- Weight-for-length z-scores

Table 4.5: Crude and adjusted model results showing the impact of infant growth measures in the previous visits on breastfeeding status in the next visit.

	Exclusive Breastfeeding		Any Breastfeeding
	(N=1422)		(N=3845)
(Observations read =N) (Observations used =n)	Crude RR (95% CI)	(Observations read =N) (Observations used =n)	Crude (RR) 95% CI
WAZ (n=977)	1.044 (1.001,1.089)	WAZ (n=2642)	1.005 (0.996, 1.013)
LAZ (n=763)	1.053 (1.02,1.087)	LAZ (n=1876)	1 (0.994, 1.006)
WLZ (n=728)	0.999 (0.968,1.033)	WLZ (n=1790)	1.004 (0.992, 1.009)

RR- risk ratios 95% CI - 95% confidence interval

Table 4.6a: Risk ratios estimated in the delayed models using repeated measurements with exclusive breastfeeding

	Exclusive breastfeeding		
(observation read N=1422) (observation used = n)	Risk ratios (95% CI)	Risk ratios (95% CI)	Risk ratios (95% CI)
Infant growth measures			
Weight-for-Age (n=876)	1.067 (1.003, 1.135)		
Length-for-Age (n=682)		1.043(0.998,1.089)	
Weight-for-Length (n=653)			1.023 (0.988,1.059)
Month			
Month6	0.329 (0.272,0.399)	0.324 (0.259,0.406)	0.322 (0.256,0.405)
Month4	0	0	0
Maternal Height	0.979 (0.960,0.999)	0.982 (0.960,1.005)	0.986 (0.963,1.01)
Birth weight	0.969 (0.846,1.110)	0.971 (0.842,1.120)	0.998 (0.873,1.141)
Race			
Non-hispanic black	0.702 (0.421,1.173)	0.741 (0.437,1.259)	0.713 (0.413,1.23)
Hispanics	0.629 (0.381,1.037)	0.928 (0.609,1.416)	0.812 (0.487,1.354)
Other	0.719 (0.560,0.923)	0.884 (0.659,1.185)	0.775 (0.577,1.02)
Non-hispanic White (ref)	0	0	0
Parity			
Multiparous	1.184 (0.546,1.368)	1.156 (1.001,1.335)	1.183 (1.020,1.373)
nulliparous (ref)	0	0	0
Pre-pregnancy Smoking			
Yes	0.865 (0.546,1.368)	0.995 (0.674,1.469)	0.881 (0.580,1.337)
No	0	0	0

All the adjusted models are adjusted for month, maternal height, birth weight, maternal race, parity, pre-pregnancy smoking status.

Table 4.6b: Risk ratios estimated in the delayed models using repeated measurements with any breastfeeding

Any breastfeeding

(observation read N=1422) (observation used = n)	Risk ratios (95% CI)	Risk ratios (95% CI)	Risk ratios (95% CI)
Infant growth measures			
Weight-for-Age (n=2324)	1.001 (0.991,1.01)		
Length-for-Age (n=1657)		0.997 (0.991,1.003)	
Weight-for-Length (n=1587)			1.002 (0.994,1.011)
Month			
Month9	1.03 (1.008, 1.053)	1.043 (1.015, 1.071)	1.042 (1.014, 1.071)
Month6	0.947 (0.919, 0.976)	0.956 (0.923,0.989)	0.953 (0.920, 0.987)
Month4	0	0	0
Maternal Height	1.002 (0.998, 1.006)	1.002 (0.997, 1.071)	1.002 (0.997, 1.007)
Birth weight	1.013 (0.988, 1.039)	1.014 (0.986, 1.044)	1.009 (0.980, 1.039)
Race			
Non-Hispanic black	0.937 (0.841, 1.045)	0.879 (0.755,1.023)	0.882 (0.756, 1.029)
Hispanics	0.912 (0.838, 0.991)	0.892 (0.796,1.000)	0.876 (0.775, 0.990)
Other	0.958 (0.895,1.025)	0.976 (0.909,1.047)	0.963 (0.889,1.043)
Non-Hispanic White (ref)	0	0	0
Parity			
Yes	1.027 (0.997, 1.057)	1.019 (0.986, 1.053)	1.015 (0.982, 1.049)
No (ref)	0	0	0
Pre-pregnancy Smoking			
Yes	0.979 (0.910, 1.053)	0.985 (0.910, 1.067)	0.975 (0.896, 1.062)
No (ref)	0	0	0

All the adjusted models are adjusted for month, maternal height, birth weight, maternal race, parity, pre-pregnancy smoking status

Table4.7: Means of anthropometric measurements and percentages of breastfeeding status throughout the 1st year of infants life

MONTH	2nd	3rd		4th	5th		6th	7th		9th	12th	
	(N= 2695) %	(N) mean (sd)	(N= 2478) %	(N= 2167) %	(N) mean (sd)	(N= 2400) %	(N= 2223) %	(N) Mean (sd)	(N= 2145) %	(N= 2187) %	(N) mean (sd)	(N= 1763) %
WAZ		(1811) -0.003 (1.12)			(1759) -0.006 (1.29)			(1605) 0.165 (1.34)			(1477) 0.305 (1.25)	
LAZ		(1432) 0.109 (1.73)			(1269) 0.014 (2.00)			(857) -0.119 (2.57)			(1111) -0.186 (2.47)	
WLZ		(1305) -0.040 (1.89)			(1233) 0.071 (2.03)			(842) 0.340 (2.03)			(1094) 0.684 (2.36)	
ExBf (Yes)	39.00		35.71	29.81		22.38	6.75		2.10	1.97		0.06
AnyBf (Yes)	68.98		60.21	57.27		55.79	48.54		47.27	45.68		25.87

ExBf= exclusive breastfeeding AnyBf = any breastfeeding
WAZ= Weight-for-age z-score WLZ=Weight-for-length z-score LAZ=Length-for-age z-score

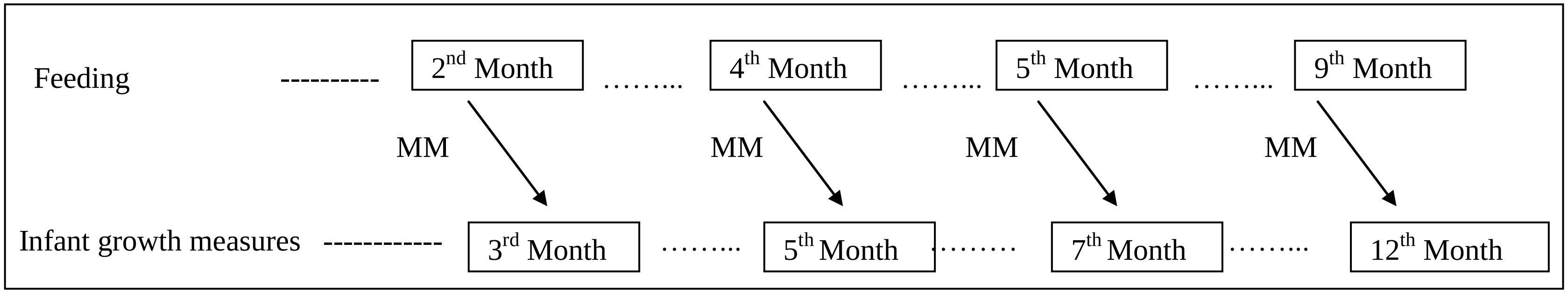

Figure 3.1: Repeated model analysis with delayed effects checking the impact of breastfeeding on infant growth

MM = Mixed Model

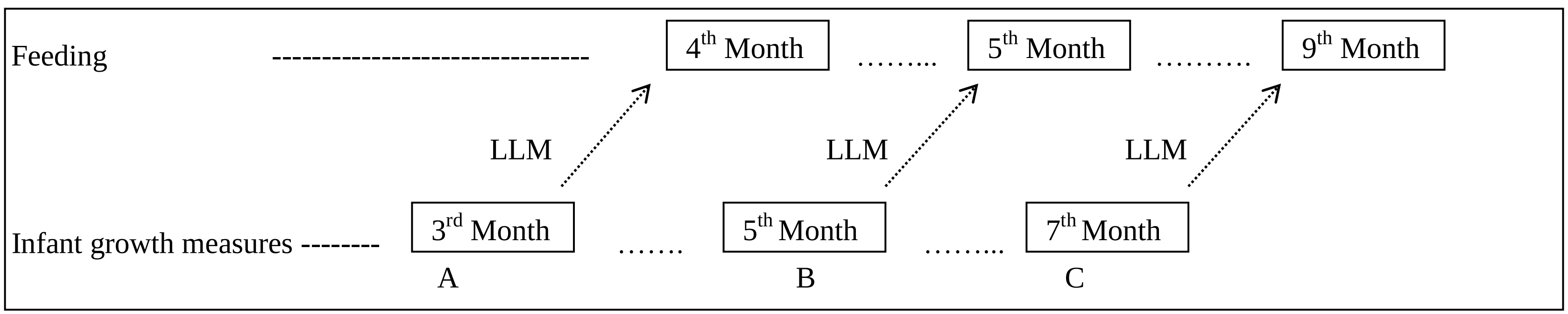

Figure 3.2: Repeated model analysis with delayed effects checking the impact of infant growth on breastfeeding
LLM= Log Linear Model
A= infants who were exclusively breastfed at 3rd month were included in the analysis
B= infants who were exclusively breastfed at 5th month were included in the analysis
C= infants who were exclusively breastfed at 7th month were included in the analysis

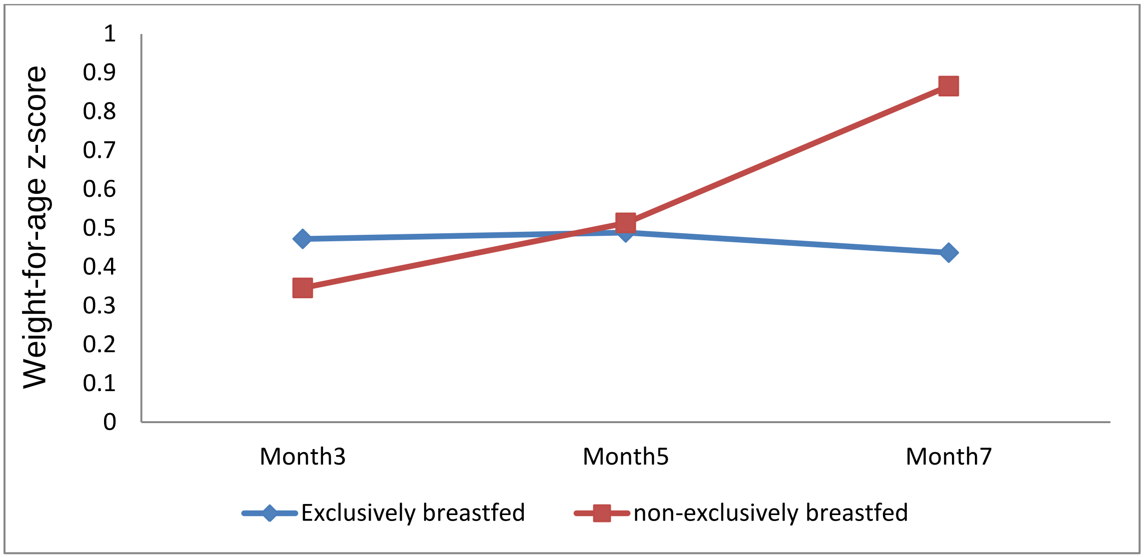

Figure 4.1: Adjusted least square mean weight-for-age z-score by exclusive breastfeeding status from month 3 to month 7.

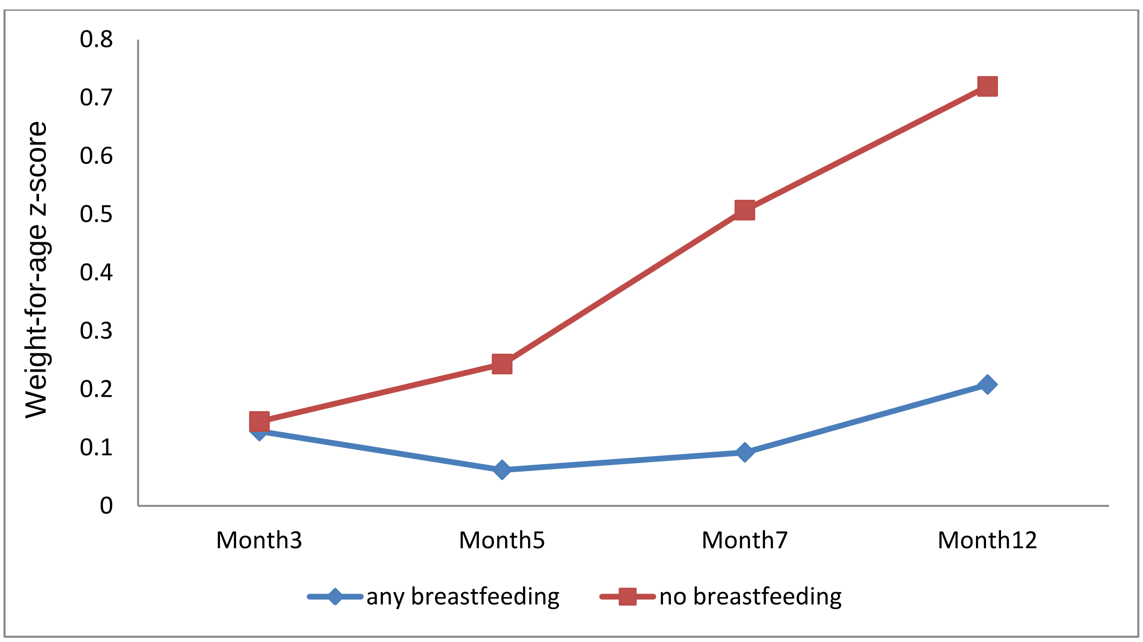

Figure 4.2: Adjusted least square mean weight-for-age z-score by any breastfeeding/no breastfeeding from 3rd month to 12th month.

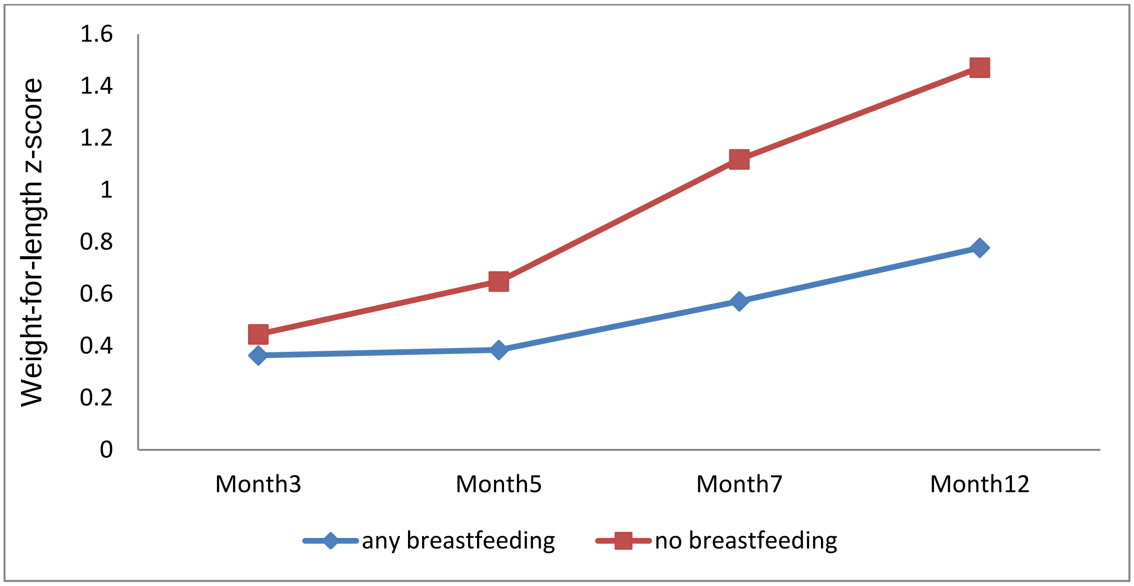

Figure 4.2: Adjusted least square mean weight-for-length z-score by any breastfeeding/no breastfeeding from 3rd month to 12th month.

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