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Association Between Infant Feeding Modes and Reflux

Pei Lin Chen

ASSOCIATION BETWEEN INFANT FEEDING MODES AND REFLLUX

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Pei-Lin Chen

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Abstract

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GER is a frequently reported health concern in neonates, which may motivate changes in infant feeding modes and addition of solid food as a milk thickening agent to sooth reflux symptom. We analyzed repeated measurements in the Infant Feeding Study II, 0505/0607, United States. A delayed model, taking the time order into account, showed that any combination of infant feeding with formula was a risk for reflux. Addition of solid food was not protective. The proportion of solid food use during the infancy increased from month 2 to month 12. Considering a reverse association (reflux → feeding), preceding reflux significantly reduced direct breastfeeding (RR=0.79, 95%CI [0.66, 0.94], p=.009). Hence, there seems to be a risk that mothers of infants with reflux stop protective breastfeeding in the following month.

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Introduction

Gastroesophageal reflux (GER) is considered to occur in more than two-thirds of healthy infants and is frequently reported by parents as health concerns in neonates (Lightdale, 2013). Gastroesophageal reflux (GER) is defined as the passage of gastric contents into the esophagus with or without regurgitation and vomiting (Badriul Hegar, 2013; Blanchard, 2013). Feeding difficulties and GER-related symptoms such as regurgitation and vomiting are main issues parents discuss with pediatricians during the routine six months infant visit (Lightdale, 2013). Regurgitation is the passage of refluxed gastric contents into the pharynx or mouth, sometimes with expulsion out of the mouth (Badriul Hegar, 2013). Parents often seek remedies for reducing the symptoms and these concerns may motivate a change in infant feeding modes or the addition of a thickening agent such as baby cereal and bean gum. GER among premature neonates is treated with acid-suppressants to prevent vomiting or regurgitation. It is estimated that 48% of premature neonates are prescribed acid-suppressants without occurring symptoms of GER or proper diagnosis (Jadcherla, 2012). About 70 to 85% of infants have been reported to suffer from regurgitation in the first 2 months of life; however, 95% of these symptoms may be spontaneously resolved after 12 to 14 months of infancy (Blanchard, 2013; Jadcherla, 2012).

Parents are concerned about feeding difficulties due to reflux which may also create uncertainties on whether their baby is feeding enough (Badriul Hegar, 2013). Feeding difficulties and GER events may be associated with weaning, switching feeding mode, or providing solid food. Moreover, feeding patterns during infancy and childhood can influence the child's health later in life (Almquist-Tangen, 2013; Nevo, 2007). Recommendations for parents for the management of GER in infants include: parental education, positional treatment, feeding techniques, and proper diet, drugs

(pokinetic agents for instance metoclopramide, domperidone, cisapride), and surgery (this is reserved for complicated cases) (Badriul Hegar, 2013; Horvath, 2008; Jadcherla, 2012; Khoshoo, 2000). Recommendation to reduce the frequency of regurgitation and vomiting includes the addition of a thickening agent to formula milk such as baby cereal, corn or potato starch, carob-bean gum, carob-seed flour, or sodium carboxymethylcellulose (Badriul Hegar, 2013; Blanchard, 2013; Jadcherla, 2012; McPherson, 2005). Infants who remain symptomatic after following these recommendations may be prescribed acid-suppressants such as a high-dose of H2 blockers and proton pump inhibitors (PPIs) to palliate GER (Barron, 2007). However, addition of solid foods may increase the risk of food allergy in early childhood (Prescott, 2008). Another concern related to the use of PPIs is the risk of lower respiratory tract infection and food allergy (Orenstein SR, 2009; PS, 2013).

Studies demonstrated that different type of feeding may show difference in physiological pattern of GER in neonates (Heacock, 1992; Hegar, 2009). Regarding feeding modes, it has been shown that infants who were exclusively breastfed were less likely to experience regurgitation than those who were partially breastfed (Badriul Hegar, 2013; Hegar, 2009). The American Academy of Pediatrics emphasizes that human milk is an optimal source of nutrition through the first year of life and recommends exclusive breastfeeding for at least six months (Eidelman, 2012). It was also shown that infants experiencing regurgitation had lower breastfeeding scores compared to babies without regurgitation (Yalçın, 2011).

We therefore hypothesize (H1) that, compared to direct (at the breast) breast feeding, other modes of infant feeding may pose a risk for developing reflux in the first 12 months of life.

In about 50% of infant in the first six month who experienced a change in feeding modes or were consuming additional solid food, the main reasons for a change in feeding modes was regurgitation or vomiting (Nevo, 2007). However, there is a lack of knowledge on whether reflux motivates parents to switch to formula or use solid food as a thickening agent for milk to prevent reflux. We also hypothesize (H2) that there also is a reverse association between reflux and infant feeding modes.

Purpose and Significance of the Study

This research seeks to find out whether specific feeding modes such as direct breastfeeding, bottle feeding, or formula feeding are related to GER. By examining the association between different feeding modes and reflux over time, we will gain an additional perspective about the temporal sequence of feeding modes and reflux and a shift in feeding modes. This analysis will also help to understand whether addition of solid food helps to reduce the prevalence of reflux.

This study is one of first to investigate the association between feeding mode and reflux using a population-wide database from the United States, controlling for potential confounders involved in reducing reflux and shifting feeding modes. The association between feeding modes and reflux will be assessed in both directions (infant feeding mode may result in reflux; and reflux may lead to changes in infant feeding modes) using repeated measurements with concurrent and delayed models.

Our research questions are as follows:

1) Is reflux associated with infant feeding mode (breastfeeding, formula feeding, bottle breast milk feeding, or mixed breastfeeding and formula feeding) in infancy? (Feeding modes → reflux)
2) Does addition of solid food (baby cereals and others) alter the association between feeding modes and reflux?

3) Is there a reverse association between reflux and infant feeding mode and solid food (Reflux → feeding modes)

Methods

The Infant Feeding Practices Survey II (IFPS II) data was collected in the United States by the Food Drug Administration (FDA) in collaboration with the Centers for Disease Control and Prevention (CDC), and was co-funded by the Office of Women's Health from the Department of Health and Human Services, the National Institute of Child Health and Human Development, the office of Dietary Supplements, the National Cancer Institute, and the Maternal and the Child Health Bureau from the Health Services and Resources Administration (Fein, 2008). It is a longitudinal study with repeated measurements. The main purpose of this study was to understand the need of improving health status of mothers and children. Data were collected from May 2005 through June 2007 (Fein, 2008).

Participants

The sampling frame for the Infant Feeding Practice Study II (IFPS II) was drawn from a nationally distributed consumer opinion panel of 500,000 households. About 4,900 pregnant women were prenatally enrolled from May 2005 to June 2007. The criteria for enrollment was as follows: women at least 18 years of age; pregnant; moderately literate; English efficiency; having a stable address for at least 11 months; a healthy mother and infant healthy at birth; full-term or near-term birth (>35 week); and a single birth. The infant had to weigh at least 5 pounds (2.26 kg) and not be in intensive care for more than 3 days (Fein, 2008; Nelís Soto-Ramírez, 2013). Approximately 3,003 of 4,900 women filled out the neonatal questionnaire (the first month questionnaire) (Fein, 2008) and of these 2,988 women provided information on feeding modes for at least 1 of 9 questionnaires that were administered during the

study period of 12 months (Nelís Soto-Ramírez, 2013). Of the latter, 2,841 (95.1%) provided information on episodes of infant's reflux in the questionnaire administered in month 2, 3, 4, 5, 6, 7, 9, 10, and 12.

Questionnaires

All mailed questionnaires were administered by the mother. In addition, a short telephone interview was conducted near the time of the infant's birth and a neonatal questionnaire was sent when the infant was around 1 month old. Nine questionnaires about infant feeding, health care, and related issues were mailed to mother every month when the infant was 2 to 7 months and then twice about every 7 weeks apart until month 12 (Fein, 2008).

Statistical Analysis

Feeding Measures

Infant feeding information was collected in all postnatal questionnaires. The questions included: "In the past 7 days, how often was your baby fed each food listed below? Include feeding by everyone who feeds the baby and include snacks and night-time feedings (per day)". The food items were listed 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. We used this information to classify infant feeding modes.

To classify direct and indirect breastfeeding, the question "Does your baby usually feed from both breasts at each feeding?" was asked. The answer selections were listed as follows: Yes, No, or baby is only fed pumped milk. To determine whether the mother solely breastfed or combined breastfeeding and bottle breast milk the following two questions were used: "Does your baby usually let go of the breast

him or herself?" was asked. The answer selections were listed as follows: Yes, both breasts, Yes, first breast only, Yes, second breast only, No. "How many times in the past 7 days was your baby fed expressed or pumped breast milk to drink.

Using these questions, we classified feeding modes into 7 categories: (1) direct breastfeeding (2) bottled breast milk feeding (3) feeding of bottled breast milk and formula (4) direct breastfeeding and formula feeding (5) mixed breastfeeding (direct breastfeeding and indirect breastfeeding) (6) mixed breastfeeding and formula, and (7) formula feeding.

Classification of feeding modes

Mode of feeding	Does your baby usually feed from both breasts at each feeding (N56)	Does your baby usually let go of the breast him or herself? (N57)	How many times in the past 7 days was your baby fed expressed or pumped breast milk to drink? (N61)	In the past 7 days, how often was your baby fed each food listed below? (N40a): Breastmilk	In the past 7 days how often was your baby fed each food listed below? (N40b): formula
Formula feeding	Instructed to skip if not breast feeding	Instructed to skip if not breast feeding	Instructed to skip	= 0	≧ 1
			0	= 0	≧ 1
Breastmilk plus formula feeding	Valid answer	Missing	≧ 1	＞0	≧ 1
	Valid answer	Missing	0	＞0	≧ 1
Bottle breast milk	Baby is fed only pumped milk	Jumped	≧ 1	>0	0
Bottle breast milk and direct breast feeding	Valid answer	No	≧ 1	>0	0
	Valid answer	Yes	≧ 1	>0	0
	Valid answer	Missing	≧ 1	>0	0
Direct breast feeding	Valid answer	No	0	>0	0
	Valid answer	Yes	0	>0	0
	Valid answer	Missing	0	>0	0
Direct breast feeding plus formula	Valid answer	No	0 0 0	>0	≧1
	Valid answer	Yes	0	>0	≧1

feeding	Valid answer	Missing	0	>0	≧1
Mixed: direct breast feeding, bottle breast milk, formula feeding	Valid answer	Yes	≧1 ≧1 ≧1	>0	≧1 ≧1 ≧1
	Valid answer	Missing	≧1		≧1
	Valid answer	No	≧1	>0	≧1

Solid-food Definition

In addition to these seven feeding modes, we also considered feeding of solid food; information on which was collected in all seven post-natal questionnaires. The question includes “How often is your baby fed which food listed below?” The choices listed as follows: baby cereal, other cereals and starches, vegetables, French fries, fruit, meat, fish or shellfish, eggs, peanut food items, dairy food items, and soy food items.

Reflux Definition

Reflux information was collected at nine time points of questionnaires in month 2, 3, 4, 5, 6, 7, 9, 10, and 12 regarding the past 2 weeks:. “Which of the following problems did your baby have during the past 2 weeks?” Possible answers addressed 13 different disorders, including reflux.

Covariates and potential confounders

To estimate the adjusted association between modes of feeding and reflux, other covariates were considered in our models as potential confounders. These were socio-demographic factors (i.e., maternal race, maternal age and education), maternal factors (maternal pre-pregnancy body mass index, and smoking status), infant’s birth weight, season of birth, and solid food. In addition, the month of the repeated measurements was included as covariate and used to provide a time order for the events.

Information of maternal race was based on the initial telephone interview and

included race/ethnicity: white, black, Hispanic, or other. Infant birth weight was collected in the Birth Screener and other information including employment status, breastfeeding attitudes and experiences, infant feeding plans and, sources of information about diet and infant feeding, and participation in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) came from the prenatal questionnaire.

All time-dependent variables (reflux, solid food, and modes of feeding) were corrected for the child's age when the questionnaire was returned.

Concurrent and delayed explanatory models

Since we have repeated measurements of infant feeding and reflux, we applied repeated measurement models, so investigate whether the association changed over time. To analyze the time order of infant feeding and reflux, we considered two models. In a concurrent model, we investigated the simultaneous occurrence of feeding (asked for the last 7 days) and reflux (asked for the last two weeks). In a delayed model, we linked the information inquired in the previous month with the response variable in the next month.

The concurrent model was used to examine whether independent variables at one time point predict the dependent variable at the same point in time (Figure 1). We tested the repeated association from month 1 to 12. For example, the 2^{nd} month modes of feeding were associated with 2^{nd} month reflux, and 3^{rd} month modes of feeding with 3^{rd} month reflux episode, and so on.

A one-month-delayed model tested whether the mode of feeding is associated with reflux event in the following month in infants (Figure 1). For example, modes of feeding in the 1^{st} month were linked with reflux in the 2^{nd} month and modes of feeding in 2^{nd} month were linked with reflux in 3^{rd} month, and so on.

Statistical Methods and Analysis Plan

SAS 9.3 (SAS Institute Inc., Cary, NC, USA) was used for our analysis. Sample characteristics focused on all infants with information on reflux (n = 2,841). Descriptive analysis was performed for all infants with information on reflux to calculate the prevalence of reflux and proportion of children who received solid food at different time points throughout the first year of the infant's life (Table 2). We considered two models (concurrent and delayed model) from month 1 to 12. The following confounders were controlled in the statistical analyses: maternal characteristics including race/ethnicity, age at pregnancy, smoking during pregnancy, body mass index, and educational status. Confounders are related to the infant included sex, birth weight, age of infant in months, and season of birth.

Our analysis focused on all infants with information on reflux (n = 2,841). The first model was a concurrent model (Figure 1). The seven modes of feeding (recalled for the past week) were tested for associations with infant reflux in the same month (recalled for the last two weeks). Since the seven modes of feeding were categorical variables therefore, we used generalized linear model (PROC GENMOD) to investigate our first research question stratified for month (2^{nd}, 3^{rd}, 4^{th}, 5^{th}, 6^{th}, 7^{th}, 9^{th}, 10^{th}, and 12^{th}) and reported the relative risks. To examine the repeated measurement of modes of feeding for reflux events, we used the generalized estimating equations (PROC GENMOD with repeated statement and log link function) and presented the relative risk (RR).

We adjusted for within-participant effects using the regular maximum likelihood method and with a first-order autoregressive working correlation structure. The first-order autoregressive covariance matrix significantly improved the fit based on the evaluation of the Akaike information criteria and the Bayesian information

criterion. Relative risks were estimated since odds ratio would be a biased estimator for the RR due to high prevalence of infant reflux. No weighting was used in any of the analyses.

The second model was a one-month delayed effect model (Figure 1), which was used to examine a potential delayed effect of feeding modes on reflux one month later. For example, reflux episodes at month 3 was tested with the month 2 mode of feeding; month 4 reflux with examine with month 3 mode of feeding, and so on. To examine this association we also applied repeated measurements models and reported the relative risk (RR).

All potential confounders were simultaneously entered into the generalized mixed models. A backward elimination process was used to retain confounders in the final model. Covariates that changed the effect of the main association by 10% or more when omitted from the model were considered as confounders.

The question of whether mode of feeding changes as a consequence of the infant's concurrent reflux (called reverse association) motivated a comparison of the occurrence of feeding modes after reflux (reflux → feeding mode). For instance, mothers whose infants had reflux events may be motivated to wane breastfeeding, switch to other feeding, or combine it with formula feeding in the belief that formula feeding may alleviate the symptoms. These analyses provide information on whether reflux may motivate the switching of infant feeding modes and will provide insights whether our assessment of reflux following specific feeding modes may be incorrect.

To address a potentially reverse association between reflux and various modes of infant feeding, we use multinomial logistic regression categorical modeling (PROC CATMOD with the direct and response statement). This analysis handles multiple dependent feeding modes: direct breastfeeding, bottle breast milk, bottle breast milk

plus formula feeding, formula feeding, direct breastfeeding plus formula feeding, mixed breastfeeding, and mixed breastfeeding plus formula feeding and estimates odds ratio of reflux related to these various responses. The CATMOD procedure uses maximum likelihood estimation of generalized logits (Stokes, 2000). In this analysis, logits are defined as the logarithm of the frequencies ratio of various different categorical and mutually exclusive outcomes. This model was examined in the one-month delayed model to tested whether previous reflux was associated with the change in infant feeding mode in the following month. For example, the 2nd month reflux episodes tested the association with 3rd month modes of feeding using PROC CATMOD. The odds ratio was presented with its 95% confidence interval. We adopted this approach to analyze a potentially reverse association and to understand the time order of events. For instance, reflux might result in a different infant feeding mode or addition of solid food.

Results

Study population.

Infants who had data on either infant feeding modes or reflux at any time point beginning from 2nd month to the 12th month comprised the analytical sample (2841/2988) of this study. Table 1 shows the distribution of the demographic characteristics of the study participants (n = 2841). The common race of the study participants was white (85%) and the main maternal age group was 25 to 29 years (34%). About 70% of the study participants had at least 1 to 3 years of higher than college degree and 45% of them had normal body mass index. About 10% of the mothers reported smoking during pregnancy.

We examined the prevalence of reflux according to maternal reports of infant's reflux episodes in different months and modes of feeding (Table 2). The prevalence of

reflux increased from month 2 to month 6 then decreased after month 6 (Table 2). The prevalence of reflux was highest in month 3 for all the modes of feeding, ranging from 19.4% to 8.1%. The highest proportion of reflux was found among infants who received bottled breast milk plus formula feeding followed by those who were fed bottled breast milk or formula (months 3-9). Except for formula feeding and solid food, the probability of all the modes of feeding decreased from month 2 to month 10 (Table 3). For solid food, we found an increasing trend from month 2 to month 10 (Table 3).

Concurrent Model

Our first research question was whether infant feeding mode (breastfeeding, formula feeding, bottle breast milk feeding, or mixed breastfeeding and formula feeding) was associated with reflux in infancy? The adjusted analysis for the repeated measurements of concurrent reflux indicated that four out of the seven feeding mode categories were risk factors for the occurrence of reflux in infancy: bottled breast milk plus formula, formula feeding, mixed breastfeeding, and mixed breastfeeding plus formula (RR = 2.64; RR = 1.98; RR = 1.52; RR = 1.73, respectively, Table 4). Among the confounders, maternal smoking during pregnancy posed a risk for reflux (RR = 1.54, 95% CI [1.04, 2.28], p = .03, Table 4). Infant's sex (boys), maternal ethnicity in Hispanic, and maternal age range from 18 to 24 had a marginal risk for concurrent reflux (RR = 1.22; RR = 0.62; RR = 0.63, respectively, Table 4).

Delayed Model

In comparison to the reference of direct breastfeeding, three modes of feeding were associated with reflux: bottled breast milk plus formula feeding, formula feeding, direct breastfeeding plus formula feeding, and mixed breastfeeding plus formula feeding (RR = 2.19; RR = 1.95; RR = 1.59, respectively, Table 4). Surprisingly,

among the confounders, a maternal age range between 18 and 25 was related to a lower risk of reflux (RR = 0.56, Table 4).

Table 5 presented the findings of the reverse association analysis using a repeated measurement approach. Compared to infants without reflux, having reflux resulted in a reduced risk of direct breastfeeding (RR = 0.79, Table 5), indicating that mothers stopped breastfeeding. Among the confounders, notably African American mothers were more likely to stop direct breastfeeding compared to non-Hispanic white (RR = 0.42, Table 5). Furthermore, infants of mothers who smoked during pregnancy were more likely to continue formula feeding, compared to mothers who do not smoked during pregnancy (RR = 1.64, Table 4). In addition, infants whose mothers smoked during pregnancy were less likely to continue a mixture of feeding (direct breast feeding, bottle breast milk, formula feeding: RR = 0.47, respectively, Table 5).

Table 6 presents the result of the reverse association analysis using multinomial regression (PROC CATMOD), stratifying by month and comparing infants with and without reflux. In the months 3, 6, 7 and 9, the infants with reflux are more likely to be formula fed, compared to the infants without reflux (OR = 1.12, OR = 1.77, OR = 2.19, and OR = 2.00 respectively Table 6). In month 6, we found that infants with reflux are 7.74 times more likely to be provided with bottled breast milk plus formula when compared to the infants without reflux.

Reflux had a marginal effect on ‘solid food’ in the reverse association analysis: infants who had reflux had higher odds of consuming solid food in the consecutive months (seen at month 3 and month 4, OR = 1.48; OR = 1.41, respectively, Table 6)

Discussion

Prevalence of reflux over the months in our analysis is high in month 2 and 3 then slowly decreased thereafter. The proportion of infants who were directly breastfed decreased from month 2 to month 6, and the tendency of formula feeding increased from month 2 to month 12. Using repeated measurement approach and compared to direct breastfeeding, any feeding mode combined with formula feeding was a risk factor for the occurrence of reflux in the next month. Our analysis showed that the addition of solid food did was not protective against reflux. The findings of the reverse association analysis using a repeated measurements approach showed decreased breast feeding in infants with reflux in the prior months when compared to the infants without reflux. This indicates that mothers did not continue directly breastfeeding if the infants have reflux. The results of the reverse association analysis using multinomial regression approach revealed that the infants with reflux are more likely to be formula-fed in the following month, when compared to those without reflux. Moreover, reflux had a marginal effect on solid food, which means that the infants with reflux were more likely to be provided with additional solid food compared to those without reflux. Overall, these findings show that mothers of the infants with reflux are more likely to discontinue direct breast feeding, and begin with formula feeding in the following month after developing reflux. Also, they are more likely to add solid food to the diet if the infant develops reflux.

The limitation of this study is that, although the sample is nationally distributed, minority groups were underrepresented (Grummer-Strawn, 2008). The socioeconomic status and educational level in this study population were higher than the national average and participants had to be English-speaking and moderately literate (Fein, 2008; Grummer-Strawn, 2008). Mothers who were less educated, younger, with a

lower socioeconomic status, participating in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), nonwhite and living in the southern region were more likely to drop out of the study (Fein, 2008; Grummer-Strawn, 2008; Nelís Soto-Ramírez, 2013).

Feeding mode was defined using the same observational variable at different points in time (Nelís Soto-Ramírez, 2013). The strength of our study was the application of seven categories of infant feeding modes which provide a more detailed classification of direct (at the breast) breastfeeding, bottled breast milk, formula and different combinations of feeding strategies. The seven categories of infant feeding modes are more likely present a realistic picture of feeding practice than a simple classification into breastfeeding or formula feeding (Nelís Soto-Ramírez, 2013). We used repeated measurements to analyze the longitudinal data (Lee, 2007). This method handles missing data and does not require the same number of observations per subject. This was very useful in our study since some participants dropped out and joined again.

The IFPS II is the largest study of infant feeding practices conducted in the United States that follows all participants through 12 months of age (Fein, 2008). As the IFPS II questionnaire asked mothers about feeding mode during the past seven days and reflux in the past two weeks, our analysis applied a one month delayed model to test the association between infant feeding mode and reflux, hence, there are minimal chances for recall bias (Grummer-Strawn, 2008).

Surprisingly, our analysis showed that bottled breast milk plus formula feeding has 119% higher risk of occurrence of reflux. This might be the due to the reason that the number of infants who were given bottled breast milk are small, and hence may limit the generalizability of our results (Nelís Soto-Ramírez, 2013). However, also

other groups with formula feeding had a higher risk of occurrence of reflux.

Wenzl et al. and Horvath et al. found that formula feeding with thickening agent is an efficient therapy for uncomplicated GER and regurgitation in infant (Horvath, 2008; Wenzl TG, 2003). However, their sample size was small (n = 14). A systematic review and meta-analysis of randomized controlled trials show that compared to standard formula, adding thickening agents to formula may results in a significant decrease of the prevalence of regurgitation (Horvath, 2008; Iacono, 2002; Wenzl TG, 2003). Whereas, the main objective of two studies primarily focused on treating reflux in infancy while compared formula feeding with formula with thickening agent feeding. Against that, a study by Hegar et al. in Indonesia demonstrated that infants with formula feeding had five to ten times more frequency of regurgitation and vomiting (Hegar , 2013). Also, Campanozzi et al. (2009) investigated the frequency of regurgitation in infants who received breast milk, compared to infants who received formula feeding and reported that breast milk is a possible protective factor for gastroesophageal reflux disease (GERD) (Campanozzi et al., 2009). Likewise, a study in Turkey by using WHO/UNICF B-R-E-A-S-T-Feeding Observation Form to evaluate the breastfeeding scores of infants demonstrating regurgitation, crying, and sleeping problem (Yalçın, 2011). Their analysis showed that babies who had regurgitation had lower breastfeeding scores than those who did not (Yalçın, 2011). Moreover, Hegar et al. (2009) showed that the prevalence of regurgitation in the exclusively breastfeeding group was less than other groups. Therefore our findings are in agreement with all the above reports that emphasize that direct breastfeeding is a protective factor for reflux.

Overall, our analysis is the first that adopted repeated measurements to investigate the association of different modes of feeding on reflux episodes in the first

12 months of infancy after controlling for confounders. The main objectives of our study was to investigate associations between infant feeding modes and reflux in healthy neonates, and our classification of infant feeding modes represents different infant feeding practices in the US.

Conclusion

Early introduction of solid foods did not protect infants against reflux; however, the tendency of infants who were consuming solid food dramatically increased. Infants with reflux have a higher odds of formula feeding, however our analysis using repeated measurement showed that formula feeding pose a higher risk of for reflux. Therefore, our results suggest that parents may be faced with misleading information on how to manage GER in their infants. Besides, out analysis showed that the addition of solid food did not alter the association between feeding models and reflux, but that infants who had reflux had a higher odds of consuming solid food in the consecutive months. It is important to inform pediatricians and health providers that adding solid food in the diet is not beneficial for infants with reflux.

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Appendix A

Table 1

Characteristics of Study Populations

		Sample with Reflux Data at Any Month (n=2841)		Sample with Reflux Data at 3-Month (n=2782)		Sample with Reflux Data At 12=Month (n=1771)	
Variables		n	%	n	%	n	%
Maternal race	White	2347	85.0	2300	85	1496	86.6
	Black	122	4.4	121	4.5	58	3.4
	Hispanic	168	6.1	163	6.1	97	5.6
	Others	126	4.5	122	4.5	77	4.5
Maternal age,y	18-24	635	22.4	615	22.2	290	16.4
	25-29	965	34.0	942	33.9	604	34.2
	30-34	787	27.8	776	28.0	533	30.1
	≧35	448	15.8	443	16.0	341	19.3
Maternal education status	< High school	81	3.1	80	3.1	47	2.9
	High school graduate	454	17.3	446	17.3	246	14.7
	College/College graduate	1828	69.6	1789	69.4	1170	69.9
	Post graduate	266	10.1	264	10.2	211	12.6
Preconception maternal body mass index, kg/m^2	Underweight(<18.5)	127	4.5	122	4.4	67	3.8
	Normal	1265	45.1	1245	45.4	794	45.5
	Overweight(25 to <30)	734	26.2	722	26.3	459	26.3
	Obese(≧30)	677	24.2	656	23.9	426	24.4
Infant's sex	Boy	1408	49.6	1380	49.7	874	49.4
	Girl	1430	50.4	1399	50.3	895	50.6
Mode of delivery	Vaginal, not induced	1077	38	1058	38.1	698	39.5
	Vaginal, induced	957	33.8	933	33.6	561	31.8
	Planned cesarian	466	16.5	460	16.6	306	17.3
	Unplanned cesarian	333	11.8	323	11.6	201	11.4

Table 1 (continued)

Characteristics of Study Populations

		Sample with Reflux Data at Any Month (n=2841)		Sample with Reflux Data at 3-Month (n=2782)		Sample with Reflux Data At 12=Month (n=1771)	
Variables		n	%	n	%	n	%
Birth weight	<2500g	48	1.7	48	1.7	25	1.4
	2500-4000g	2467	86.9	2414	86.9	1535	86.8
	>4000g	323	11.4	317	11.4	209	11.8
Maternal smoking during pregnancy	Yes	269	9.6	262	9.5	143	8.1
	No	2559	90.4	2507	90.5	1621	91.9
Infant's birth season	Fall	1096	38.6	1076	38.7	660	37.3
	Spring	31	1.1	30	1.1	16	0.9
	Summer	661	23.3	652	23.5	429	24.3
	Winter	1050	37.0	1021	36.7	664	37.5

Table 2

Prevalence of Maternal Reports of Infant's Reflux Episode in Different Modes of Feeding (n = 2841)

	Month 2 (n=1704) % (n/n)	Month 3 (n=2216) % (n/n)	Month 4 (n=1998) % (n/n)	Month 5 (n=2090) % (n/n)	Month 6 (n=2007) % (n/n)	Month 7 (n=1959) % (n/n)	Month 9 (n=1872) % (n/n)	Month 10.5 (n=1680) % (n/n)	Month 12 (n=1018) % (n/n)
Prevalence of reflux stratified by mode of feeding	9.2	10.1	8.9	7.7	6.6	5.4	4.9	3.8	1.6
Bottled breast milk	4.8 (1/21)	15.8 (3/19)	7.1 (1/14)	13.3 (2/15)	6.7 (1/15)	7.7 (1/13)	6.7 (1/15)	0 (0/10)	0 (0/5)
Bottled breast milk and formula	7.5 (3/40)	19.4 (7/36)	11.4 (4/35)	14.7 (5/34)	12.5 (3/24)	8.3 (1/12)	12.5 (2/16)	0 (0/11)	0 (0/4)
Formula	10.9 (63/580)	11.5 (101/875)	11.3 (100/886)	9.9 (92/962)	8.2 (83/1007)	6.5 (69/1062)	5.1 (56/1092)	3.9 (41/1047)	2.1 (12/571)
Direct breastfeeding and formula	8.8 (15/171)	8.1 (18/221)	4.3 (7/164)	3.3 (6/180)	5.5 (10/182)	6.3 (12/189)	6.4 (10/157)	4.4 (6/137)	0 (0/47)
Mixed breastfeeding	9.6 (34/354)	9.5 (42/440)	9.7 (34/351)	7.2 (24/330)	6.0 (15/250)	3.8 (8/209)	3.3 (5/152)	6.0 (6/100)	0 (0/49)
Mixed breastfeeding and formula	9.8 (20/204)	9.3 (20/215)	9.0 (17/188)	7.7 (14/182)	2.1 (3/146)	3.1 (3/98)	4.2 (3/71)	6.5 (3/46)	0 (0/17)
Direct breastfeeding	6.6 (22/334)	8.3 (34/410)	6.1 (22/360)	4.4 (17/387)	5.0 (19/383)	3.2 (12/376)	4.3 (16/369)	2.4 (8/329)	2.2 (7/325)
Solid food	15.3 (33/216)	11.7 (52/444)	10.3 (90/875)	7.5 (119/1579)	6.5 (121/1872)	5.4 (105/1950)	5.0 (94/1892)	3.8 (66/1740)	1.5 (27/1763)

Table 3

The Probability of Different Infant Feeding Mode and Addition of Solid Food Stratified by Month (n = 2841)

	Month 2 (n=1704) % (n/n)	Month 3 (n=2216) % (n/n)	Month 4 (n=1998) % (n/n)	Month 5 (n=2090) % (n/n)	Month 6 (n=2007) % (n/n)	Month 7 (n=1959) % (n/n)	Month 9 (n=1872) % (n/n)	Month 10.5 (n=1680) % (n/n)	Month 12 (n=1018) % (n/n)
Bottled breast milk	1.2 (21/1704)	0.9 (19/2216)	0.7 (14/1998)	0.7 (15/2090)	0.8 (15/2007)	0.7 (13/1959)	0.8 (15/1872)	0.6 (10/1680)	0.5 (5/1018)
Bottled breast milk plus formula	2.4 (40/1704)	1.6 (36/2216)	1.7 (35/1998)	1.6 (34/2090)	1.2 (24/2007)	0.6 (12/1959)	0.9 (16/1872)	0.7 (11/1680)	0.4 (4/1018)
Formula	34.0 (580/1704)	39.5 (875/2216)	44.2 (886/1998)	46.0 (962/2090)	50.2 (1007/2007)	54.1 (1062/1959)	58.4 (1092/1872)	62.3 (1047/1680)	56.1 (571/1018)
Direct breastfeeding plus formula	10.0 (171/1704)	10.0 (221/2216)	8.3 (164/1998)	8.6 (180/2090)	9.1 (182/2007)	9.7 (189/1959)	8.4 (157/1872)	8.5 (137/1680)	4.6 (47/1018)
Mixed breastfeeding	20.8 (354/1704)	19.9 (440/2216)	17.8 (351/1998)	15.8 (330/2090)	12.5 (250/2007)	10.7 (209/1959)	8.1 (152/1872)	6.0 (100/1680)	4.8 (49/1018)
Mixed breastfeeding plus formula	12.0 (204/1704)	9.7 (215/2216)	9.5 (188/1998)	8.7 (182/2090)	7.3 (146/2007)	5.0 (98/1959)	3.8 (71/1872)	2.7 (46/1680)	1.7 (17/1018)
Direct breastfeeding	19.6 (334/1704)	18.5 (410/2216)	17.9 (360/1998)	18.5 (387/2090)	19.1 (383/2007)	19.2 (376/1959)	19.7 (369/1872)	19.6 (329/1680)	31.9 (325/1018)
Solid food	12.4 (216/1747)	19.8 (445/2252)	42.1 (876/2079)	74.0 (1580/2134)	92.1 (1875/2037)	98.5 (1951/1980)	99.7 (1894/1900)	99.5 (1765/1769)	99.5 (1742/1751)

Table 4

The Risk Ratios (RR) Estimated in Concurrent and Delayed Models using Repeated Measurements of Reflux in Infancy from 2 to 12 Months.

	Concurrent Model (Events/Trials=536/14169)			Delayed Model (Events/Trials=357/12399)		
Risk Factors	Risk Ratio	95% Confidence Interval	p value	Risk Ratio	95% Confidence Interval	p value
Different modes of feeding with direct breastfeeding as reference						
Bottled breast milk	1.33	0.45, 3.92	0.61	1.26	0.40, 3.97	0.69
Bottled breast milk and formula	2.64	1.39, 4.99	0.003^{+++}	2.19	1.11, 4.33	0.025^{+++}
Formula	1.98	1.42, 2.76	$<0.01^{+++}$	1.95	1.39, 2.74	$<0.01^{+++}$
Direct breastfeeding and formula	1.20	0.77, 1.85	0.42	1.51	0.98, 2.31	0.06^{+}
Mixed breastfeeding	1.52	1.07, 2.15	0.018^{+++}	1.08	0.73, 1.58	0.71
Mixed breastfeeding and formula	1.73	1.13, 2.64	0.01^{+++}	1.59	1.40, 2.42	0.033^{+++}
Solid food	1.23	0.94, 1.60	0.14	1.21	0.86, 1.70	0.28

$^{+}$ $p<0.10$; $^{++}$ $p<0.05$; $^{+++}$ $p<0.01$

Table 4 (continued)

The Risk Ratios (RR) Estimated in Concurrent and Delayed Models using Repeated Measurements of Reflux in Infancy from 2 to 12 Months.

	Concurrent Model (Events/Trials=536/14169)			Delayed Model (Events/Trials=357/12399)		
Risk Factors	Risk Ratio	95% Confidence Interval	p value	Risk Ratio	95% Confidence Interval	p value
Sex (female as reference)	1.22	0.98, 1.51	0.07^{+}	1.24	0.97, 1.58	0.09^{+}
Maternal ethnicity (White as reference)						
Black	0.79	0.41, 1.51	0.47	0.67	0.35, 1.28	0.22
Hispanic	0.62	0.36, 1.07	0.08^{+}	0.56	0.28, 1.14	0.11
Other	0.57	0.28, 1.17	0.12	0.51	0.26, 0.99	0.05^{++}
Maternal smoking during pregnancy (non-smoking as reference)	1.54	1.04, 2.28	0.03^{+++}	1.29	0.84, 2.02	0.25
Maternal age (25-<30 as reference)						
18-25	0.63	0.38, 1.04	0.07^{+}	0.56	0.32, 0.99	0.04^{++}
30-35	1.01	0.67, 1.52	0.95	1.23	0.77, 1.96	0.38
>35	1.40	0.66, 2.99	0.38	1.95	0.84, 4.52	0.12
Sibling	0.96	0.91, 1.01	0.13	0.97	0.92, 1.02	0.23

$^{+}$ p<0.10; $^{++}$ p<0.05; $^{+++}$ p<0.01

Table 5

Reverse association *- Risk Ratios (RR) Estimated in Delayed Models using Repeated Measurements of Each Feeding Mode Associated with Reflux in Infancy from 2 to 12 Months. Exposure: Reflux, Outcome: Infant Feeding Modes (Infants Who Do Not Have Reflux at Each Feeding Mode as Reference)*

	Bottled Breast Milk Events/Trials=117/12543		Bottled breast milk and formula Events/Trails =187/12543		Formula Events/Trails =5354/12543		Direct breastfeeding and formula Events/Trails =1239/12543		Mixed breastfeeding Events/Trails =1982/12543		Mixed breastfeeding and formula Events/Trails =1012/12543		Direct breastfeeding Events/Trails =2652/12543		Solid food Events/Trails =7400/12399	
Risk Factors	Risk Ratio 95 % Confidence Interval	p	Risk Ratio 95 % Confidence Interval	p	Risk Ratio 95 % Confidence Interval	p	Risk Ratio 95 % Confidence Interval	p	Risk Ratio 95 % Confidence Interval	p	Risk Ratio 95 % Confidence Interval	p	Risk Ratio 95 % Confidence Interval	p	Risk Ratio 95 % Confidence Interval	p
Reflux	1.01 0.62, 1.64	.96	1.30 0.70, 2.41	.40	1.03 0.96, 1.11	.38	1.08 0.80, 1.44	.62	0.82 0.65, 1.02	.08^{+}	0.97 0.72, 1.32	.87	0.79 0.66, 0.94	.009^{+++}	1.15 0.82, 1.63	.42
Sex (female as reference)	1.44 0.74, 2.79	.28	1.24 0.83, 1.86	.29	0.96 0.89, 1.03	.04^{++}	0.98 0.83, 1.16	.81	1.09 0.95, 1.26	.21	0.98 0.83, 1.17	.86	0.95 0.83, 1.08	.40	1.40 1.19, 1.65	<.01^{+++}
Maternal ethnicity (White as reference)																
Black	2.33 0.77, 7.06	.13	1.77 0.6, 3.65	.12	1.20 1.04, 1.38	.01^{+++}	1.39 0.93, 2.08	.11	0.60 0.36, 1.01	.05^{++}	1.38 0.89, 2.11	.14	0.42 0.24, 0.72	.0017^{++}	2.74 1.77, 4.24	<.01^{+++}
Hispanic	2.63 0.97, 7.09	.06^{+}	0.85 0.34, 2.15	.73	1.02 0.87, 1.21	.80	1.62 1.20, 2.18	.0015^{+++}	0.72 0.51, 1.01	.06^{+}	1.32 0.97, 1.79	.08^{+}	0.64 0.46, 0.89	.008^{+++}	0.77 0.52, 1.12	.16
Other	1.15 0.32, 4.13	.83	0.83 0.28, 2.12	.70	0.80 0.63, 1.00	.05^{++}	1.85 1.32, 2.59	.0004^{+++}	0.68 0.47, 0.99	.05^{++}	1.12 0.79, 1.58	.53	1.03 0.70, 1.52	.87	0.60 0.40, 0.91	.017
Maternal smoking during pregnancy			0.62 0.18, 2.08	.44	1.64 1.48, 1.80	<.01^{+++}	0.92 0.66, 1.27	.61	0.47 0.30, 0.73	.0007^{+++}	0.94 0.63, 1.39	.76	0.40 0.26, 0.62	<.01^{+++}	1.45 1.04, 2.03	.03^{++}
Sibling	1.34 0.63, 2.45	.53	1.41 0.94, 2.11	.09^{+}	1.05 0.97, 1.13	.22	0.99 0.84, 1.18	.92	1.05 0.91, 1.21	0.55	0.98 0.82, 1.17	.81	0.96 0.84, 1.09	.53	0.98 0.95, 1.02	.29
Maternal age (age range 25- <30 as reference)																
18- <25	0.64 0.28, 1.46	.29	1.01 0.57, 1.78	.98	1.46 1.31, 1.62	<.01^{+++}	0.95 0.73, 1.24	.69	0.63 0.49, 0.81	.0003^{+++}	0.99 0.75, 1.33	.97	0.71 0.57, 0.88	.001^{+++}	1.30 0.92, 1.85	.13
30- <35	0.46 0.19, 1.14	.09^{+}	1.27 0.79, 2.04	.31	1.07 0.96, 1.19	.23	1.26 1.02, 1.55	.03^{++}	0.86 0.73, 1.01	.07^{+}	1.11 0.90, 1.37	.34	0.79 0.67, 0.92	.0033^{++}	0.90 0.67, 1.22	.50
>35	0.45 0.14, 1.43	.17	0.88 0.47, 1.68	.71	1.08 0.95, 1.22	.23	1.37 1.07, 1.75	.01^{+++}	0.79 0.64, 0.97	.03^{++}	1.31 1.03, 1.67	.03^{++}	0.80 0.66, 0.96	.097	0.97 0.55, 1.70	.91

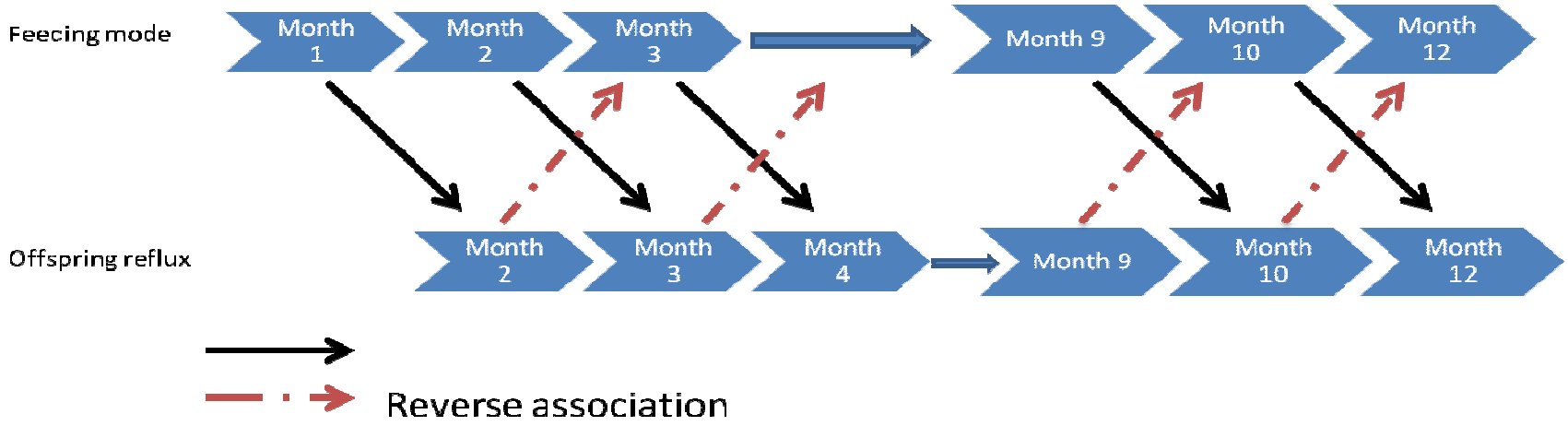
$^{+}$ p<0.10; $^{++}$ p<0.05; $^{+++}$ p<0.01

Table 6

***Reverse association**-Odds Ratio and their 95% Confidence Interval of Reflux Related to Different Modes of Feeding with Direct Breastfeeding as Reference (Delayed Model).*

Previous month occur reflux episode and the following month feeding	Bottle Breast milk OR, 95% CI p	Bottle breast milk and formula OR, 95% CI p	Formula OR, 95% CI p	Direct breastfeeding and formula OR, 95% CI p	Mixed breastfeeding OR, 95% CI p	Mixed breastfeeding and formula OR, 95% CI p	Direct breastfeeding as reference	Solid food OR, 95% CI p
Month2 reflux → Month 3 feeding	0.74, [0.09, 5.88] 0.78	1.60, [0.52, 4.97] 0.41	1.12, [0.69, 1.82] 0.04^{++}	0.98, [0.49, 1.51] 0.60	0.86, [0.49, 1.51] 0.60	0.49, [0.20, 1.21] 0.12	1	1.48, [0.97, 2.26] 0.07^{+}
Month3 reflux → Month 4 feeding	0.97, [0.12, 7.79] 0.98	1.35[0.38, 4.77] 0.64	1.51, [0.95, 2.42] 0.08^{+}	1.05, [0.51, 2.16] 0.89	1.32, [0.76, 2.29] 0.32	1.28, [0.66, 2.47] 0.46	1	1.41, [0.96, 2.06] 0.07^{+}
Month4 reflux → Month 5 feeding	1.22, [0.15, 9.85] 0.86	2.43, [0.77, 7.67] 0.13	1.56, [0.95, 2.54] 0.08^{+}	0.85, [0.38, 1.89] 0.68	1.28, [0.70, 2.34] 0.42	0.98, [0.45, 2.12] 0.95	1	1.32, [0.79, 1.62] 0.50
Month5 reflux → Month 6 feeding	1.29, [0.16, 10.4] 0.81	1.77, [0.38, 8.15] 0.47	1.77, [1.06, 2.96] 0.03^{++}	0.54, [0.20, 1.47] 0.23	1.40, [0.72, 2.73] 0.32	0.83, [0.32, 2.12] 0.95	1	1.44, [0.91, 2.29] 0.12
Month6 reflux → Month 7 feeding	2.46, [0.29, 20.59] 0.41	7.74, [1.45, 41.19] 0.02^{++}	2.19, [1.17, 4.10] 0.01^{+++}	2.39, [1.08, 5.29] 0.23	1.82, [0.80, 4.14] 0.15	1.00, [0.28, 3.63] 1.00	1	0.85, [0.42, 1.72] 0.64
Month7 reflux → Month 9 feeding	2.07, [0.25, 17.19] 0.50	2.42, [0.29, 20.27] 0.42	2.00, [1.04, 3.85] 0.04^{++}	1.48, [0.56, 3.90] 0.43	1.32, [0.48, 3.64] 0.59	1.58, [0.43, 5.85] 0.49	1	0.57, [0.13, 2.48] 0.45
Month9 reflux → Month 10 feeding	<0.001	<0.001	1.50, [0.77, 2.92] 0.24	1.76, [0.69, 4.49] 0.24	1.20, [0.37, 3.85] 0.76	1.27, [0.27, 5.92] 0.76	1	0.004 ^{ns}
Month10 reflux → Month 12 feeding	<0.001	<0.001	1.01, [0.49, 2.05] 0.98	0.59, [0.08, 4.63] 0.61	1.03, [0.23, 4.74] 0.97	<0.001	1	0.12, [0.01, 1.02] 0.05^{++}

$^{+}$ p<0.10; $^{++}$ p<0.05; $^{+++}$ p<0.01



Figure

Repeated Model Analyses with Delayed Effects for Infant Who Occur Reflux Symptom in the Following Month.

Appendix B

Dear Dr. Karmaus and Pei Lin,
Thank you for your quick response. I think this will answer your next question also Dr. Karmaus:

The IRB Administrator has reviewed your Initial review request for the study, "Association between infant reflux cause early stage exposed to solid food and infant growth " and the additional information provided in this email and it is determined that since you are 1) conducting research involving only coded private information of which 2) the information was not collected for your currently proposed research, and 3) the investigator cannon readily ascertain the identity of individuals in the study, it is determined that this is not Human Subjects Research and 45 CFR 46 does not apply.
Neither IRB review nor IRB approval is required.
With best regards,

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