INFANT FEEDING PRACTICES AND ASTHMA IN CHILDREN AGED 6 MONTHS TO 5 YEARS USING A PROPENSITY SCORE APPROACH

Chukwuemeka E. Ogbu[1], Samuel Fongue[2], Stella C. Ogbu[3], Russell S. Kirby[1]
[1]College of Public Health, University of South Florida, Tampa, Florida, United States of America
[2]College of Medicine and Health Sciences, Abia State University, Uturu, Nigeria
[3]Department of Biological Sciences, East Tennessee State University, Johnson City, Tennessee, United States of America

SUMMARY

Objectives: We examined the association between exclusive breastfeeding, early introduction of feeding formula, early weaning, and asthma in children aged six months to five years in a sample of non-institutionalized US children using a propensity score approach.

Methods: Our study used data from the National Survey of Children's Health (2012–2018) of 3,820 children with physician-diagnosed asthma aged 6 months to 5 years. Propensity score matching (PSM) was applied to control selection bias with age, sex, race, birth weight, Federal Poverty Level, parent's education, and parent smoking history used as covariates in PSM. The total number in the matched sample was 6,904 (3,452 non-asthmatics; 3,452 asthmatics). Matched and unmatched samples were analysed using the χ^2 test and multiple logistic regression.

Results: Exclusive breastfeeding was protective against asthma in the pre-matching (AOR 0.72; 95% CI: 0.54–0.97; $p = 0.03$) and post-matching (AOR 0.66; 95% CI: 0.55–0.81; $p < 0.001$) samples. Formula feeding before 6 months was associated with asthma in unmatched (AOR 1.38; 95% CI: 1.15–1.66; $p < 0.001$) and matched (AOR 1.31; 95% CI: 1.16–1.47; $p < 0.001$) sample. Early weaning before 6 months was associated with asthma in unmatched (AOR 1.62; 95% CI: 1.35–1.54; $p < 0.001$) and matched sample (AOR 1.37; 95% CI: 1.23–1.54; $p < 0.001$).

Conclusion: Public health systems should continue to recommend the implementation of the World Health Organization exclusive breastfeeding guideline in developed countries. Asthma interventions in children under two years should continue to emphasize exclusive breastfeeding to reduce the incidence of infant asthma.

Key words: asthma, breastfeeding, formula feeding, propensity score matching

Address for correspondence: C. E. Ogbu, College of Public Health, University of South Florida, 13201 Bruce B. Downs Blvd, MDC56 Tampa, FL 33612, USA. E-mail: ogbu@usf.edu

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INTRODUCTION

Asthma is one of the leading causes of years lived with disability (1). Globally it is among the leading causes of burden of disease (1). Asthma is the leading chronic disease among children aged 0–17 years, and it is more common in children than in adults (2). The prevalence rate of asthma in children 0–4 years was 4.4% in 2018 and showed a declining trend in this age group compared to children 5–17 years after 2018 (3). Studies demonstrate that over 50% of children diagnosed with asthma later in life developed symptoms before the age of five, making this age group critical in preventing long-term asthma into adulthood (4). Moreover, diagnosis in this age group is difficult and complicated due to difficulty obtaining an objective asthma diagnosis (4). Despite the general declining trend, the chronicity of asthma with the resulting progression to childhood asthma can result in children's impaired physical and social functioning, making asthma prevention in under five a significant public health problem (5).

The long-standing debate on whether breastfeeding reduces the risk of asthma continues. The World Health Organization (WHO) states that exclusive breastfeeding reduces infant mortality due to common respiratory illnesses like pneumonia and asthma (6). While breast feeding is important for the growth, nourishment and promotion of motor and sensory growth and development of the infant as well as protecting the baby against infectious and chronic diseases, its effects on childhood asthma has been mixed. Most major studies found a positive effect of breastfeeding on childhood asthma (7–9). Some other studies did not find a protective effect (10, 11). Earlier studies found that exclusive breastfeeding had a preventive effect on the early development of asthma up to 2 years of age (12) and a dose-response reduction in asthma risk with increased breastfeeding duration over 4 months to 9 months (7, 13). A meta-analysis found a significant protective association between breastfeeding and asthma. However, the strength of the association found in the ages 0–2 years diminished over time (14), while another meta-analysis reported a protective effect of breastfeeding duration and reduced asthma risk in children aged 5–18 years especially in medium and low-income countries (15). These studies reported significant heterogeneities due to differences in study designs and overall quality of evidence due to the selection biases inherent in the observational nature of most of the studies used in the meta-analysis.

Further, the WHO classifies an infant who has received formula milk as "partially breastfed" if the infant had ever received formula milk before six months (16). Formula-fed infants have lower bacterial diversity and an altered intestinal microbiota in the first few weeks of life associated with an increased risk of asthma, leading to the suggestion that favourable gut colonization through continued breastfeeding may promote tolerance as well as protection (17, 18). Moreover, the introduction of infant formula earlier than 14 weeks of age is associated with a higher risk of non-atopic asthma, twice greater risk of not fully breastfeeding at 1–2 months among women intending to breastfeed exclusively, and exposure to potent allergens contained in most cow milk infant formulas (19–21).

Randomized controlled trials in epidemiology provide the best evidence of cause and effects relationship, however, ethical reasons preclude its use in infant feeding research. Therefore, observational studies remain the mainstay of examining the effects of breastfeeding on health outcomes. A major limitation of observational methods is that treatment is not randomized. There is a possibility of selection bias associated with the baseline characteristics of cases and controls rather than the exposure itself (22). More so, confounders in many observational studies are controlled through multivariable analysis, however, this method is not without its problems (23). Given these limitations, research is needed to elucidate the effect of breast and formula feeding practices on diagnosing asthma in children under five years of age using robust methods that account for selection bias.

Unlike randomized controlled trials, observational studies are prone to selection bias. For this reason, the objective of this study was to examine the association between exclusive breastfeeding, formula feeding, and early weaning practice on asthma in children six months to five years using a different approach that controls selection biases and confounders more efficiently. Propensity score matching (PSM) has been applied in this research to measure the effect of different infant feeding practices on asthma (22, 23).

MATERIALS AND METHODS

Participants and Procedures

We used 2012, 2016, and combined 2017 and 2018 data from the National Survey of Children's Health (NSCH) to answer the research question. The datasets were selected because they were the most recent data cycles of NSCH. The NSCH is a cross-sectional study of non-institutionalized US children aged 0–17 years. It is sponsored by the Health Resources and Services Administration's Maternal and Child Health Bureau (HRSA MCHB) since 2001 (24). The NSCH surveys the physical and emotional health of children, emphasizing factors related to child well-being, health care, family interactions, parental health, neighbourhood characteristics, and school and after-school experiences. Information is collected from parents or guardians who know about the child's health. The NSCH is administered online and by mail. Randomly selected addresses from households across the US were mailed instructions to access the survey online; some addresses also received a paper version of the screening questionnaire. After two reminder letters and postcard reminders to complete the survey by web, those households who had not accessed the online survey were mailed a paper screening questionnaire (24).

Our dataset consisted of children sampled from 50 states of the United States in 2012, 2016, 2017 and 2018. The overall weighted response rates ranged from 37.4% to 43.1%. Breastfeeding information and practices were only collected in children aged six months to five years. The NSCH received approval from the National Center for Health Statistics Research Ethics Review Board, and all participants provided informed consent.

This study is exempt from full institutional review because the NSCH is a public use dataset that does not include personal information. A detailed description of the data, sampling method and other analytical guidelines are available elsewhere (25).

Measurement

Outcome and Exposure

A single item was used to ascertain the history of childhood asthma. Respondents were asked: "Has a doctor or other health professional ever told you that your child has asthma?". The child was considered to have childhood asthma if the parent's response was affirmative to this item. Self-reported physician diagnoses are reliable and valid measures of asthma status in both children and adults (26). Asthma status is the outcome of interest.

Infant feeding practices were assessed through these three questions: "Was this child exclusively breastfed for six months?", "Was breastfeeding stopped in this child earlier than six months?" and "Was this child fed formula milk earlier than six months of age?". Responses were converted to binary variables (yes vs. no) responses.

Covariates

The questionnaire item ascertained household smoking "Does anyone in the household use tobacco?" and responses were recorded as "yes" and "no". Birth weight was assessed with the survey question "How much did he or she weigh when born?" and categorized as low birth weight if birth weight was $< 2{,}500$ grams or normal weight if birth weight was $\geq 2{,}500$ grams. Other covariates are age in years, sex (male or female), race/ethnicity (Hispanic, white non-Hispanic, black non-Hispanic, multiracial/other races), socioeconomic status variables like the educational status of an adult in the household (high school or lower or some college degree or higher) and household Federal Poverty Level (FPL) (less than 100% FPL, 100–199% FPL, 200–399% FPL, $\geq$400% FPL. This information was collected at the time of the survey.

Statistical Analyses

Propensity score matching was used to match an asthma case to a control case to control selection bias and confounding. PSM utilizes the predicted probability of group membership, e.g., treated versus untreated group, based on a specified observed predictor, usually obtained from logistic regression to create a counterfactual group (27, 28). Defined as the conditional probability of being treated given the covariates of interest, propensity score (PS) can balance covariates in the two groups, thereby reducing bias (27). Asthma status was used as the outcome in the PSM model.

Socio-demographic (age, gender and race), socioeconomic (parent education, Federal Poverty Level), and confounding factors (birth weight, parent smoking status) were used as covariates in the PSM model by using the 1 : 1 "greedy nearest neighbour" matching in which each treated unit (in this case children who reported asthma) is sequentially matched with the control case (children who reported no asthma) (27). Covariate assessment using histogram and mean standardized differences in the PS match was used to assess the reasonability of the match between cases or controls (on a variable basis) and ascertain whether propensity scores fall within the limits of the standard mean differences of 0.2. Standardized mean differences of up to 0.2 are optimal (29). Rao-Scott Chi square test was used to compare the covariate distribution before and after matching.

Multivariable logistic regression was then used to analyse the association between asthma in children six months to five years and infant feeding practices in the unmatched and matched samples. Three models were created with asthma as the response variable and exclusive breastfeeding, early formula introduction, and breastfeeding duration as explanatory variables, respectively. We tabulated the results of the descriptive analysis as percentages and results of logistic regression models as odds ratios (ORs) and 95% confidence intervals (CIs) for all independent variables in the models. Interaction effects were not statistically significant between each of the predictors and covariates in the three models. The statistical hypothesis was tested using $p < 0.05$ as the level of significance. All analyses were done in SAS 9.4 statistical software (Cary, NC).

Table 1. *Descriptive statistics showing covariate imbalance before and after matching by propensity score*

Covariates	Study population N = 54,972		p-value	PS-matched sample N = 6,904		p-value
	Asthma			Asthma		
	No	Yes		No	Yes	
	n (%)	n (%)		n (%)	n (%)	
Age (years)						
Less than 1	4,651 (10.1)	82 (2.5)	< 0.001	77 (2.2)	77 (2.2)	1
1	8,958 (18.5)	335 (9.1)		298 (8.6)	298 (8.6)	
2	9,291(17.7)	503 (13.5)		471 (13.6)	471 (13.6)	
3	9,734 (18.2)	769 (19.9)		684 (19.8)	684 (19.8)	
4	9,374 (18.1)	980 (26.4)		877 (25.4)	877 (25.4)	
5	9,144 (17.4)	1,151 (28.4)		1,045 (30.3)	1,045 (30.3)	
Race						
White non-Hispanic	33,750 (52.6)	1,989 (39.3)	< 0.001	1,869 (54.1)	1,869 (54.1)	1
Hispanic	6,740 (24.4)	585 (24.4)		523 (15.2)	523 (15.2)	
Black non-Hispanic	3,300 (11.0)	637 (24.7)		553 (16.0)	553 (16.0)	
Multiracial/others	6,731 (12.0)	550 (11.6)		507 (14.7)	507 (14.7)	
Sex						
Female	25,286 (49.5)	1,457 (39.9)	< 0.001	1,310 (38.0)	1,310 (38.0)	1
Male	25,847 (50.5)	2,361 (60.1)		2,142 (62.1)	2,142 (62.1)	
Parent education						
College or higher	13,103 (31.7)	1,358 (41.6)	< 0.01	1,277 (37.0)	1,273 (36.9)	0.920
High school or lower	36,378 (68.3)	2,281 (58.4)		2,175 (63.0)	2,179 (63.1)	
Federal Poverty Level						
Less than 100% FPL	19,216 (29.0)	1,094 (20.4)	< 0.001	1,016 (29.4)	1,025 (29.7)	0.966
100–199% FPL	15,630 (27.9)	1,051 (24.3)		974 (28.2)	978 (28.3)	
200–399% FPL	8,928 (21.4)	733 (22.7)		651 (18.9)	656 (19.0)	
≥ 400% FPL	7,378 (21.7)	942 (32.6)		811 (23.5)	793 (23.0)	
Birth weight						
Normal birth weight	45,363 (90.9)	3,131 (85.5)	< 0.001	2,985 (86.5)	2,968 (86.0)	0.553
Low birth weight	4,039 (9.1)	529 (14.5)		467 (13.5)	484 (14.0)	
Parent smoking						
No	41,456 (83.1)	2,808 (77.4)	< 0.001	2,611 (75.6)	2,604 (75.4)	0.845
Yes	9,067 (16.9)	973 (22.6)		841 (24.4)	848 (24.6)	

RESULTS

PSM Match Characteristics

Table 1 compares the unmatched and matched samples including the general characteristics of participants and the summary of results before and after PSM. The total number of participants was 54,972 (51,152 non-asthmatics; 3,820 asthmatics) in the unmatched sample. After propensity score matched with exact age, race, sex, and birth weight, parent smoking, parent education, and Federal Poverty Level in the PSM model, the total number in the matched sample was 6,904 (3,452 non-asthmatics; 3,452 asthmatics). The Chi-square analysis test revealed significant differences in the pre-match samples compared to the insignificant differences in the PS-matched samples indicating that the post-match sample was balanced.

Infant Feeding Practices and Asthma

Exclusive breastfeeding was negatively associated with asthma among children aged six months to five years (Table 2). In the unadjusted model, children who were exclusively breastfed were 53% and 30% less likely to have asthma compared to children not exclusively breastfed in the pre-matched sample (OR 0.47; 95% CI: 0.41–0.53; $p<0.001$) and in the post-matched sample (OR 0.70; 95% CI: 0.59–0.84; $p<0.001$). Breastfeeding remained protective in the unmatched sample (AOR 0.72; 95% CI: 0.54–0.97; $p=0.03$) and PS-matched sample (AOR 0.66; 95% CI: 0.55–0.81; $p<0.001$) after controlling for the effect of age, sex, race, birth weight, Federal Poverty Level, parent's education, and parent smoking history in the model.

Formula feeding earlier than six months was associated with increased asthma in both samples unadjusted and adjusted models. Specifically, infants who were introduced formulas had 38% higher odds of asthma in the adjusted unmatched sample (AOR 1.38; 95% CI: 1.15–1.66; $p<0.001$) and 31% increased odds of asthma in the PSM sample (AOR 1.31; 95% CI: 1.16–1.47; $p<0.001$) after controlling for age, sex, race, weight, FPL, parent education, smoking, and breastfeeding status. The odds of asthma were higher in children weaned before six months in the unmatched sample (AOR 1.62; 95% CI: 1.35–1.54; $p<0.001$) and matched sample (AOR 1.37; 95% CI: 1.23–1.54; $p<0.001$) compared to children breastfed more than six months in the adjusted model.

DISCUSSION

Our study demonstrated a significant and robust association between exclusive breastfeeding and asthma in a nationally representative sample of US children aged six months to five years. Mothers who exclusively breastfed their children were less likely to report asthma than those who did not in our PS-matched sam-

Table 2. *Multivariable logistic regression of predictors against breastfeeding practices in children aged 6 months to 5 years, National Survey of Children's Health (NSCH), 2012–2018*

Breastfeeding practices	Unmatched sample			
	Unadjusted model		Adjusted model	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Exclusive breastfeeding (model 1)[a]				
Not exclusively breastfed	Ref.		Ref.	
Exclusively breastfed	0.47 (0.41–0.53)	<0.001	0.72 (0.54–0.97)	0.03
Formular feeding (model 2)[b]				
Formular fed at 6 months or after or never	Ref.		Ref.	
Formular fed earlier than 6 months	1.64 (1.38–1.94)	<0.001	1.38 (1.15–1.66)	<0.001
Early breastfeeding stop (model 3)[b]				
Stopped 6 months or longer	Ref.		Ref.	
Stopped less than 6 months	1.79 (1.53–2.09)	<0.001	1.62 (1.35–1.94)	<0.001
Propensity score matched sample				
Exclusive breastfeeding (model 1)[a]				
Not exclusively breastfed	Ref.		Ref.	
Exclusively breastfed	0.70 (0.59–0.84)	<0.001	0.66 (0.55–0.81)	<0.001
Formular feeding (model 2)[b]				
Formular fed at 6 months or after or never	Ref.		Ref.	
Formular fed earlier than 6 months	1.25 (1.12–1.40)	<0.001	1.31 (1.16–1.47)	<0.001
Early breastfeeding stop (model 3)[b]				
Stopped 6 months or longer	Ref.		Ref.	
Stopped less than 6 months	1.26 (1.14–1.40)	<0.001	1.37 (1.23–1.54)	<0.001

[a]Adjusted model controlled for age, sex, race, birth weight, Federal Poverty Level, parent education, and smoking
[b]Adjusted model controlled for age, sex, race, birth weight, Federal Poverty Level, parent education, smoking, and ever breastfeeding

ple. The association remained significant in our pre-match and post-match sample after adjusting for several socioeconomic, demographic, and confounding factors. Our study is consistent with the results of two meta-analyses which found that exclusive breastfeeding was protective against asthma. Dogaru et al. (14), in their meta-analysis of 117 articles and after stratifying by age, reported a strong protective association at ages 0–2 with diminished influence over time and suggested a positive association of breastfeeding with reduced breastfeeding asthma. Another meta-analysis corroborated their studies that reported a reduced risk of asthma for children aged 5–18 years, especially in medium and low-income countries (15). In a cohort study result, children exclusively breastfed for four or more months had less asthma and a significant reduction in asthma risk if partially breastfeed for six months or more (13). To evaluate if age modified the effect of exclusive breastfeeding on asthma, we tested the moderating effect of age on the association between exclusive breastfeeding and asthma in our unmatched and matched samples, and it was not significant. This could be because the sample size was small in both unmatched and matched samples to drive the interaction.

Another important finding of our study is that children fed formula milk earlier than six months were more likely to report asthma than those fed formula milk after six months, even after adjusting for ever breastfed status. Similarly, children whose parents stopped breastfeeding before six months had higher odds of asthma when adjusted for ever breastfed status.

Formula feeding has generated controversy in public health. Recent microbiome research suggests that seeding of the infant's gut with beneficial microbe enables the establishment of a healthy infant microbiome structure that protects the child from diseases during the life course (18, 30). Bacterial diversity and compositional changes are related to a dose-response proportion of daily breast milk even after introducing solid foods (30).

Our study utilized the NSCH database, an extensive and comprehensive survey of children's health in the United States; 2012, 2016, 2017 and 2018 NSCH study datasets were combined to increase the sample size of children aged six months to five years with a history of asthma and is representative of the diversity of the United States. Therefore, results from this dataset reflect the current state of children's health in the United States. Unlike in clinical trials, where patients are randomized to treatment and a control group, observational studies are liable to confounding factors and selection bias (23). Therefore, PSM was applied in this study to control confounding by age, race, and sex and control selection bias. This study is relevant because it is one of the first attempts to use PSM to analyse the relationship between infant feeding practices and asthma in children under five years.

Our study has several limitations. Despite the aim of propensity score matching to transform observational studies into a quasi-experimental design, the study design is still cross-sectional, and we cannot make cause and effects inferences. PSM does not eliminate all biases that confounders might have introduced, as it is possible to have several unmeasured biases in this study. Reporting bias may exist as parents may not be adequately trained to recognize asthma symptoms or consult healthcare providers early enough. Moreover, children under five years of age are more prone to physician asthma misdiagnosis, and therefore the actual prevalence estimates of asthma may be understated or overstated in this study. The cross-sectional nature of this study also limited the scope of the secondary data analysis as some putative risk factors were not included in the survey. Despite the shortcomings of our study, this research contributes to the literature. It confirms the findings from other cross-sectional studies that breastfeeding is protective against asthma in a population of children matched by age, sex, race, birth weight, parent education, parent smoking history, and Federal Poverty Level.

CONCLUSION

In summary, exclusive breastfeeding decreased the odds of asthma diagnosis while formula feeding before six months of age and early weaning before six months increased the odds of asthma in children aged six months to five years using the propensity score approach. Public health systems should continue to recommend and implement the WHO exclusive breastfeeding guideline. Asthma interventions in children less than two years should continue to emphasize breastfeeding to reduce the incidence of asthma in the population.

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Conflict of Interests

None declared

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