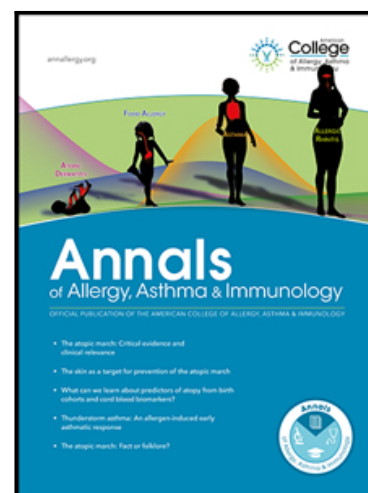


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The association between duration of breastfeeding and childhood asthma outcomes



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Title: The association between duration of breastfeeding and childhood asthma outcomes

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Key words: child, asthma, breastfeeding, wheeze

Abbreviations:

CANDLE: Conditions Affecting Neurocognitive Development and Learning in Early Childhood

TIDES: The Infant Development and Environment Study

GAPPS: Global Alliance to Prevent Prematurity and Stillbirth

ISAAC: International Study of Asthma and Allergies in Childhood

Abstract

Background: Postnatal exposures, including breastfeeding, may influence asthma development.

Objective: To investigate the association between breastfeeding duration and child asthma.

Methods: We studied 2,021 mother-child dyads in the ECHO PATHWAYS consortium of prospective pregnancy cohorts (GAPPS, CANDLE, TIDES). Women reported the duration of any and exclusive breastfeeding and child asthma outcomes during follow-up at child age 4–6 years. Outcomes included current wheeze (last 12 months), ever asthma, current asthma (having ≥ 2 of current wheeze, ever asthma, medication use in past 12-24 months) and strict current asthma (ever asthma with current wheeze and/or medication use in past 12-24 months). We used multivariable logistic regression to assess associations (odds ratios [OR] and 95% confidence intervals [95%CI]) between breastfeeding and asthma outcomes adjusting for potential confounders. We assessed effect modification by mode of delivery, infant sex and maternal asthma.

Results: Among women, 33%, 13%, 9% and 45% reported 0<2, 2-4, 5-6, and >6 months of any breastfeeding, respectively. The duration of any breastfeeding had a protective linear trend with ever asthma but no other outcomes. There was a duration-dependent protective association of exclusive breastfeeding and child asthma outcomes (e.g., current asthma adjusted OR [95% CI]: 0.64 [0.41, 1.02], 0.61 [0.38, 0.98], and 0.52 [0.31, 0.87] for durations of 2-4, 5-6, and >6-months respectively, compared to <2 months). For exclusive breastfeeding, protective associations were stronger in dyads with children born by vaginal versus cesarean delivery although interactions were not significant.

Conclusion: Longer duration of exclusive breastfeeding had a protective association with child asthma.

Introduction

Asthma is a chronic disease of the airways, characterized by episodes of bronchial hyperresponsiveness, airway obstruction, and inflammation.^{1, 2} Because most children develop symptoms before age six, examining early life exposures may inform investigations aimed at elucidating underlying pathophysiology and efforts to prevent or modify disease severity.³ Prenatal and early life exposures, such as infant diet, may

influence the subsequent development of asthma through effects on the developing immune and pulmonary systems.^{4, 5} For example, human milk contains maternal microbiota, oligosaccharides, immune factors, nutrients, hormones, and growth factors that together influence lung and immune system development including shaping of the infant microbiome which includes the signaling of multiple molecular and epigenetic pathways.⁶⁻⁹ Thus, breastfeeding, including duration and dose, is an important potentially modifiable factor in asthma development.

Although the association between breastfeeding and asthma is an active area of research, there have been some inconsistencies in findings and gaps where further investigation is warranted. For example, some studies have found that breastfeeding is protective against asthma in children,¹⁰⁻¹³ while others have found increased¹⁴ or no association with asthma.¹⁵ These studies varied in study population, exposure assessment, asthma characterization and age at assessment. Moreover, given that associations may be modified by biological variables (e.g., maternal asthma status and child sex) or environmental factors (e.g., mode of delivery), it is important to systematically assess these associations for effect modification to delineate potential underlying mechanisms and guide practice recommendations.¹⁶⁻¹⁹ Additionally, examining both breastfeeding duration and exclusiveness can provide insight into potential duration-response relationships.¹¹ Lastly, broader inclusion of diverse populations in studies of breastfeeding and asthma is important as racial/ethnic disparities in both breastfeeding rates and early childhood asthma have been reported.^{1, 6, 20, 21} Using harmonized data from three, racially and geographically diverse US

pregnancy cohorts, we examined whether both breastfeeding duration and exclusiveness is inversely associated with child asthma. We further assessed for effect modification by maternal asthma, child sex, and mode of delivery.

Methods

Study Population

This investigation included maternal-child dyads enrolled in the NIH ECHO-PATHWAYS consortium which includes three prospective pregnancy cohorts: the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) study, The Infant Development and Environment Study (TIDES), and the Global Alliance to Prevent Prematurity and Stillbirth (GAPPS). CANDLE and TIDES cohorts have been described previously.^{22, 23} In brief, CANDLE enrolled women in Shelby County (Memphis), TN who were between 16 and 40 years, able to speak and understand English, and had a low medical risk, singleton pregnancy that were between 16- and 28-weeks gestation.²² Between 2006 and 2011, of 1503 women enrolled in CANDLE, 1455 had live births and were active in the study at delivery, and 1157 dyads participated in the study visit at about child age 4-6 years.²² The TIDES study recruited women ≥ 18 years who were in their first trimester (< 13 weeks), able to read and write English and whose pregnancy was not medically threatened.^{23, 24} Women were recruited across four sites: University of Minnesota Medical Center (Minneapolis, MN); University of California-San Francisco Medical Center (San Francisco, CA); University of Rochester Medical Center (Rochester, NY); and University of Washington (Seattle,

WA).^{23, 24} Overall, 969 women enrolled in TIDES between 2011 and 2013. Of the women active in TIDES after enrollment, 749 had live births and 544 dyads participated in follow-up at child age 4-6 years.^{23, 24} Lastly, the original GAPPS study enrolled healthy pregnant women. It conducted visits throughout pregnancy and, in a subset, visits in the immediate postpartum period, after which the participants were not engaged in further research activities and infants were not recruited into the GAPPS study. The ECHO PATHWAYS study recontacted women who previously participated in GAPPS based on eligibility criteria (child age, recruitment site, consent to future contact, and biospecimen availability), and enrolled children into the age 4-6 year visit which was the first PATHWAYS study visit for GAPPS²⁵ and included 423 dyads. In total, 2124 dyads from the three cohort studies participated in follow-up. Children older than 7.5 years at follow-up were excluded from the current analysis (N=19). Of the 2,105 dyads that completed study follow-up ≤ 7.5 years, 2,021 had breastfeeding data (4% missing, n=84) and were included in this study.

All cohorts collected psychosocial and demographic characteristics, medical history, and biospecimens prenatally. Postnatally each cohort conducted in-person clinic visits and collected demographic, psychosocial, and medical history data that included assessment of child wheeze and asthma outcomes. The women provided informed consent for themselves and their children. This current study was approved by the University of Washington (UW) IRB.

Breastfeeding Exposures

The duration of *any* and *exclusive* breastfeeding were assessed via questionnaire at approximately 4-6 years (mean age 4.5 years, interquartile range 4.1-5 years). The first exposure was duration of *any* breastfeeding. We captured the duration of *any* breastfeeding as none to <2 months, 2-4 months, 5-6 months and >6 months based on responses to the questions “Was your child ever breast fed?” and “How long was your child breastfed?” For women who reported breastfeeding, we defined duration of *exclusive* breastfeeding, as <2 months, 2-4 months, 5-6 months and >6 months based on responses to the categorical question “How long was your child breastfed without adding formula, juices or other foods?” Exclusive breastfeeding for about 6 months is recommended by the American Academy of Pediatrics and the World Health Organization and data was captured in these categories based off these recommendations.^{26, 27}

Child respiratory outcomes

Child wheeze and asthma outcomes were ascertained using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire and additional questionnaires that assessed asthma-specific medication use and diagnosis during the 4 to 6-year visit.²⁸⁻³⁰ Four wheeze/asthma outcomes were considered in this analysis.²⁸ **Current wheeze** was defined as affirmative responses to the questions: (1) “Has your child ever had wheezing or whistling in the chest at any time in the past” and (2) “Has your child ever had wheezing or whistling in the chest in the last 12 months?” **Ever asthma** was

defined as an affirmative response to the question: “Has your child ever had asthma?”

Current asthma was defined as reporting two out of the following three: 1) *current wheeze*, 2) ever asthma, or 3) asthma-specific medication use (defined as asthma-specific medication use in the previous 12 months for CANDLE and GAPPS [yes/no] and free-text reporting of asthma or asthma symptoms and medication use for this condition in the previous 24 months for TIDES).³¹

We defined **strict current asthma** to identify children who were diagnosed with asthma and had current symptoms as measured by reported prevalent symptoms or medication use. The definition included children who responded affirmatively to the question, “Has your child ever had asthma?” (i.e., *ever asthma*) and those who had *current wheeze* and/or asthma-specific medication use.

Covariates

Information obtained at enrollment included maternal age (years), race (White, Black and Other), education level (<high school, high school or General Educational Development (GED), college or technical school and some graduate work or graduate/professional degree), smoking during pregnancy (yes, no), and parity (0, ≥ 1). Data collected at birth included delivery type (vaginal, cesarean), sex (male, female) and estimated gestational age (EGA) (days). Maternal history of asthma (yes, no), as one measure of a familial predisposition to develop asthma, was assessed at the GAPPS 4-6-year visit, the CANDLE 4-year visit and the TIDES 6-year visit.

Statistical Analysis

Cohort characteristics were summarized by descriptive statistics including frequencies and proportions for categorical data and median and interquartile ranges [IQR:25th, 75th] for continuous variables. Child and maternal characteristics were compared by breastfeeding category using chi-square and Kruskal-Wallis rank sum test, as appropriate. We used multivariable logistic regression to calculate adjusted odds ratios (aOR) and 95% confidence intervals (95% CI) for child wheeze and asthma outcomes at age 4-6 years using separate regressions for duration of *any* and *exclusive* breastfeeding.^{32, 33} The covariates in the main model were selected *a priori* and included site, maternal age, race, education, prenatal smoking, asthma history, parity, and mode of delivery as well as child EGA and sex. We also performed a mixed effects logistic regression with random effects for site.

A priori selected effect modifiers were maternal asthma, mode of delivery and child sex. We performed interaction analyses with cross-product terms to examine if associations between breastfeeding exposures and childhood wheeze/asthma outcomes were modified by these factors. The p interaction reflects the test of the cross-product term, formally testing the interaction between breast feeding and factor (e.g.: maternal asthma). Its value was considered significant at the level of 0.05. To assess the stability of the pooled analysis to the influence of any one cohort, we completed a series of sensitivity analyses in which, in turn, each of the three cohorts was excluded.

Additionally, we performed a linear test for trend across exposure groups using the estimated midpoint (months) of each breastfeeding category (*any*: 1 month, 3 months, 5.5 months, and 9 months; *exclusive*: 1 month, 3 months, 5.5 months, and 6.5 months)

as linear predictors in logistic regression models. R version 3.6.3 was used for all analysis and statistical tests were considered significant at the level of 0.05.

Results

Maternal and Child Characteristics

Overall, 2,021 dyads with breastfeeding exposure and child follow-up at about 4-6 years were included (Table 1). For the pooled cohort, 38% of women identified as Black, 52% as White, and 6% as Hispanic/Latina. Forty-four percent of women reported a high school education or less. The CANDLE cohort included 63% Black women as compared to GAPPS with 2% and TIDES with 11%. Additionally, in the CANDLE cohort 58% of women had high school as the highest level of educational attainment, while that proportion was 31% in GAPPS and 32% in TIDES. Overall, few women reported smoking during pregnancy (CANDLE 9%, GAPPS 3% and TIDES 5%).

Among children, 50% were female, 42% were first born and 34% were born by c-section. The median EGA at birth was 39.29 weeks (IQR: 38.43, 40.14). The median age of children at the 4-6-year visit was 4.5 years (IQR: 4.1, 5). Overall, the prevalence of child wheeze/asthma outcomes were 16%, 12%, 12% and 9% for *current wheeze*, *ever asthma*, *current asthma*, and *strict current asthma*, respectively. By cohort, children in CANDLE had higher prevalence of all outcomes relative to TIDES and GAPPS (Table 1).

Overall, the percentage of women reporting breastfeeding durations of 0<2, 2-4, 5-6, and > 6 months was 33%, 13%, 9%, and 45%, respectively (Figure 1). Most women who breastfed their child >6 months were White (68%) and had more than a high school education (78%). Across cohorts, TIDES had the largest percentage of women who breastfed >6 months (71%), followed by GAPPS (62%) and CANDLE (27%). A larger proportion of women in CANDLE reported never breastfeeding their index child (32%) compared to TIDES (8%) and GAPPS (6%). Among children ever breastfed (N=1553), the percentage of mothers reporting breastfeeding durations of <2, 2-4, 5-6, and > 6 months was 24%, 24%, 28% and 24%, respectively (Figure 1). TIDES had the highest percentage of children (31%) exclusively breastfed for >6 months.

Breastfeeding duration and child wheeze/asthma outcomes

We first assessed the association between duration of *any* breastfeeding and child wheeze/asthma outcomes in unadjusted and multivariable analyses (eTable 1). In multivariable analyses, breastfeeding duration was not associated with child wheeze/asthma outcomes (Figure 2). Although the overall adjusted association was not statistically significant for the outcome *ever asthma*, there was a significant linear trend towards protection ($p_{\text{linear}}=0.034$). In models with *ever asthma* as the outcome, longer duration of any breastfeeding trended with decreased odds (aOR [95%CI], including 0.79 [0.49, 1.24]; 0.72 [0.42,1.25]; and 0.65 [0.43,0.97] for 2- 4 months, 5-6 months, and >6 months, respectively, when compared to children in the none to <2 months category (Figure 2).

Next, we investigated unadjusted and multivariable associations between duration of *exclusive* breastfeeding and child wheeze/asthma outcomes (eTable 2) and several of the associations were statistically significant after confounder adjustment (Figure 2). For example, longer duration of *exclusive* breastfeeding was associated with decreased odds of *current asthma* (aOR [95%CI]) of 0.64 [0.41, 1.02], 0.61 [0.38, 0.98], and 0.52 [0.31, 0.87] for 2-4 months, 5-6 months, and >6 months, respectively, when compared to children in the exclusively breastfed <2 months (Figure 2). Additionally, protective associations for *current wheeze*, *ever asthma* and *strict current asthma* were found for comparisons between the referent and >6 months of exclusive breastfeeding (Figure 2). Linear trends also were observed with longer duration of exclusive breastfeeding (*current wheeze* $p_{\text{linear}}=0.061$, *ever asthma* $p_{\text{linear}}=0.005$, *current asthma* $p_{\text{linear}}=0.009$, *strict current asthma* $p_{\text{linear}}=0.018$).

We next examined effect modification of the association of breastfeeding exposures and child respiratory outcomes. For mode of delivery, there were no statistically significant interactions between the association of duration of *any* breastfeeding and child wheeze/asthma outcomes (eTable 3). When assessing for effect modification between *exclusive* breastfeeding duration and mode of delivery on child wheeze/asthma outcomes, protective associations were consistently stronger in dyads with vaginal deliveries compared to cesareans, although interactions were not statistically significant. For example, in the subset of children who were born vaginally, those who were exclusively breastfed either 2-4 months, 5-6 months or >6 months had aORs [95% CI]

for *current asthma* of 0.48 [0.26, 0.86]; 0.46 [0.25, 0.86] and 0.29 [0.14, 0.61], respectively, compared to children exclusively breastfed <2 months. In the subset of children who were born by cesarean, those who were exclusively breastfed for either 2-4 months, 5-6 months or >6 months had aORs [95%CI] for *current asthma* of 0.95 [0.47, 1.92]; 0.84 [0.41, 1.72] and 0.98 [0.47, 2.06], compared to children exclusively breastfed <2 months ($p_{\text{interaction}} = 0.12$).

When assessing for effect modification by history of maternal asthma, *any* breastfeeding duration was associated with protective associations for current asthma in children whose mothers did not have asthma (e.g., aOR: 0.58 (95% CI: 0.37, 0.92) for >6 months vs. 0-2 months), but not among children whose mothers had asthma (e.g., aOR: 1.49 (95% CI: 0.79, 2.80) for >6 months vs. 0-2 months) ($p_{\text{interaction}} = 0.013$). Odds ratios followed a similar direction for other outcomes; however interactions were not significant ($p_{\text{interaction}} = 0.12 - 0.18$). There was no evidence of effect modification by maternal asthma history for *exclusive* breastfeeding duration (all $p_{\text{interaction}} > 0.67$), wherein we observed inverse (protective) relationships regardless of maternal asthma history. However, estimates for those with maternal asthma ($n = 279$) lacked precision (e.g., aOR *current asthma* = 0.76 [95% CI: 0.32, 1.81]). There was no indication of effect modification by infant sex, in the association of any (all $p_{\text{interaction}} > 0.05$) or exclusive (all $p_{\text{interaction}} > 0.20$) breastfeeding duration and child asthma outcomes

Sensitivity analyses

Lastly, we completed sensitivity analyses, leaving one cohort out of the pooled analysis at a time (eFigure 1 and eFigure 2). Relative to the original pooled analysis, results did not appreciably change in models that excluded TIDES or GAPPS. When excluding our

largest cohort, CANDLE, associations were generally consistent with the pooled analysis but were notably less precise due to decreased sample size. The largest differences due to CANDLE exclusion were seen for associations between any breastfeeding duration and *strict current asthma* and *current wheeze*. Although the exclusive breastfeeding point estimates had wide confidence intervals and included the null, estimates were consistent with the pooled analysis allowing us to assert that results were robust to site exclusion. Additionally, as a sensitivity analysis, we performed a mixed effects logistic regression model with site as a random effect and results were consistent.

Discussion

Prenatal and early life dietary exposures are potential modifiable factors that may influence asthma development in children.^{7,8} In this large, socioeconomically, and racial/ethnically diverse cohort of over 2,000 mother-child dyads, we found evidence of protective associations between longer duration of *exclusive* breastfeeding and child asthma outcomes. These associations were robust even after adjustment for many established confounders. In contrast, duration of *any* breastfeeding, which included dyads with either partial or exclusive breastfeeding, was not strongly associated with subsequent development of wheeze or asthma, apart from *ever asthma*.

This work builds upon previous investigations of infant diet and asthma. Studies that examined duration of breastfeeding have reported protective associations. Specifically,

a cohort study of ~880 Australian and Swedish children with a family history of asthma found that infants breastfed ≥ 3 months had lower relative risk of asthma at 5 years and 8 years.³⁴ In addition, a Dutch study of over 5,000 dyads, found that shorter duration of breastfeeding (<2 months) was associated with *current asthma* and early wheezing (≤ 3 years old) and less *exclusive* breastfeeding (≤ 4 months) was associated with early wheezing; however this study did not evaluate for potential modification by factors such as maternal asthma.¹¹ In contrast, in a Belarus follow-up study of a cluster-randomized controlled trial focused on breastfeeding promotion where the intervention was associated with longer duration of breastfeeding at three months, there was no associated decrease in asthma or wheeze¹⁴. Of note, the prevalence of atopic outcomes was several-fold lower than those seen in most U.S. populations, so it is unclear how generalizable these results are to our study population.¹⁴ Despite these divergent findings, recent meta-analyses support the protective effect of more versus less breastfeeding on the development of asthma.^{35, 36} Specifically, the meta-analyses showed that the protective association is strongest in children 0-2 years old and only modest after age 7.³⁵

In addition to the primary analyses, we assessed for effect modification in the associations between duration of *any* and *exclusive* breastfeeding and childhood asthma/wheeze outcomes by maternal asthma history, infant sex or delivery type. For maternal asthma history as a potential effect modifier, we observed protective associations for *any* breastfeeding duration among dyads without maternal asthma but not among dyads with maternal asthma, although this interaction reached statistical

significance only for the current asthma outcome. We did not observe evidence of effect modification by maternal asthma history for exclusive breastfeeding. Taken together, future studies should consider how the dose of breastfeeding, presumably higher in exclusive breastfeeding, influences asthma risk in children with a familial predisposition to develop asthma. When considering effect modification by child sex, although there was not statistically significant interaction, prospective studies with larger samples across the different breastfeeding duration strata may provide insights as studies have had mixed results^{16, 17, 37}

We also investigated the interaction of mode of delivery which has a known influence on establishing the gut microbiome postnatally⁵ and growing evidence suggests that the microbiome perturbation may be associated with asthma risk.³⁸⁻⁴⁰ Although the p-values for interaction did not reach statistical significance, there is the suggestion of a stronger protective association between duration of *exclusive* breastfeeding and asthma in children born vaginally compared to those born by c-section. While *exclusive* breastfeeding for approximately the first 6 months is recommended for infants except in rare cases, these novel findings highlight the potential additional benefit of vaginal delivery and *exclusive* breastfeeding in child respiratory health. Interestingly, an investigation of 673 dyads suggested that mode of delivery and exclusive breastfeeding modified the association between maternal atopy and allergic outcomes in young children.⁴¹ Thus, our investigation of exposures that modify the association of breastfeeding and child asthma suggests a potential mechanistic area of exploration as

well as supports future investigations with larger sample sizes and that assess the role of antibiotic prophylaxis during caesareans.⁴²

Literature suggests that human breast milk plays a key role in disease prevention and the subsequent development of chronic conditions like necrotizing enterocolitis, diabetes and asthma⁵. Previous studies have suggested that breastmilk components such as oligosaccharides influence the developing immune system by promoting a healthier gut microbiome composition and the immune system in turn modulates lung development through specific cytokines, immunoglobins and hormones^{5,8,9}. Consequently, the changing gut microbiome through multiple molecular pathways and epigenetic modifications affect the development of allergic disease.³⁸ While the mechanisms are not fully delineated, previous work in the field and the trend toward a dose response in many of the analyses in this current study, suggest a prolonged and high dose of breast milk exposure is beneficial and pivotal for child asthma prevention.

There are strengths and limitations to consider in this study. Strengths include the well-characterized, diverse study population that resulted from pooling three prospective pregnancy cohorts. By including Black children who historically have experienced lower rates of breastfeeding, our work can potentially inform targeted interventions that address the breastfeeding disparity in the United States.⁶ Moreover, this study assessed duration of breastfeeding and potential duration-dependent dose response,

controlled for key confounders, and tested for potential effect modification by maternal asthma, child sex and mode of delivery.

Limitations include ascertaining maternal report of breastfeeding at child age 4 to 6 which may result in misclassification. However, previous research studies have largely supported validity and reliability of maternal recall of infant feeding practices.⁴³⁻⁴⁵ For example, maternal recollection of breastfeeding was accurate in two studies that examined recall six years after delivery and in a Norwegian study that examined recall after 20 years.⁴³ van Zykl and co-authors found accurate recall of *exclusive* breastfeeding duration after 10 years ($r = 0.70$, $p < 0.05$).⁴⁵ An additional limitation included the inability to differentiate between breastmilk from direct breastfeeding and breastmilk fed through a bottle.^{46, 47} Although the outcomes are based on parent-report, a validated questionnaire was used and is widely used to identify asthma and wheeze.³⁰ In addition, there may be unmeasured confounding to consider for further cautious interpretation.

Lastly, this study strengthens current breastfeeding recommendations which reflect recent analysis that show lower risk of asthma with more versus less breastfeeding.^{35, 48} Although guidelines recommend not delaying the introduction of solid foods to prevent atopic disease, the strongest evidence applies to peanut allergy, where in a randomized trial (RCT) including high-risk infants between 4-11 months, infants randomized to consume peanuts in the first 60 months of life had reduced risk of peanut allergy.⁴⁹ A follow-up study to the RCT did not find that breastfeeding duration was impacted by early introduction of peanut containing foods.⁵⁰

In summary, in this racially diverse cohort study, we found that longer duration of *exclusive* breastfeeding was associated with decreased odds of child asthma. Our study extends the understanding of the association between breastfeeding duration and child respiratory health and informs future investigations of asthma and lung function in older children and how exposures may modify associations.

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Table 1. Characteristics of dyads (births, 2006-2015)

	CANDLE N=1149	GAPPS N=418	TIDES N=538	Total N=2105
Maternal				
Race/ethnicity, n (%)				
White	360 (31)	331 (83)	384 (72)	1075 (52)
African-American	720 (63)	8 (2)	57 (11)	785 (38)
Other	69 (6)	62 (15)	90 (16)	221 (10)
Hispanic or Latina	21 (2)	59 (14)	46 (9)	126 (6)
Age (years)*	26 (22-30)	31 (27-34)	31 (28-35)	28 (24-33)
Education, n (%)				
Less than high school	130 (11)	16 (4)	33 (6)	179 (9)
GED or high school diploma	536 (47)	110 (27)	85 (16)	731 (35)
Technical school/college	346 (30)	180 (43)	165 (31)	691 (33)
≥Some graduate work	136 (12)	109 (26)	252 (47)	496 (24)
Maternal asthma, yes n (%)	199 (18)	75 (18)	82 (17)	356 (17)
Prenatal smoking, yes n (%)	104 (9)	12 (3)	24 (5)	140 (7)
Child				
Gestational Age (days)*	274 (269-279)	274 (264-281)	277(270-284)	275 (269-281)
Age at follow-up (years)*	4.6 (4.1-4.6)	5.5 (5.1-6)	4.5 (4.3-4.8)	4.5 (4.1-5)
Sex, female n (%)	577 (50)	204 (49)	282 (52)	1063 (50)
Firstborn, yes n (%)	456 (40)	137 (33)	286 (54)	879 (42)
Delivery Route, Vaginal n (%)	718 (63)	265 (63)	395 (73)	1378 (66)
Current wheeze [†] , yes n (%)	218 (19)	53 (13)	52 (10)	323 (16)
Ever asthma, yes n (%)	168 (15)	33 (8)	40 (7)	241 (12)
Current asthma [‡] , yes n (%)	182 (16)	39 (10)	29 (5)	250 (12)
Strict current asthma [§] , yes n (%)	136 (12)	24 (6)	29 (6)	189 (9)

*Median (interquartile range), [†]Current wheeze: wheezing/whistling in the chest in the past 12 months, [‡]Current asthma: (2 of 3) ever asthma, current wheeze and/or medication use in past 12-24 months, [§]Strict current asthma: ever asthma and current wheeze, and/or medication use in the past 12-24 months

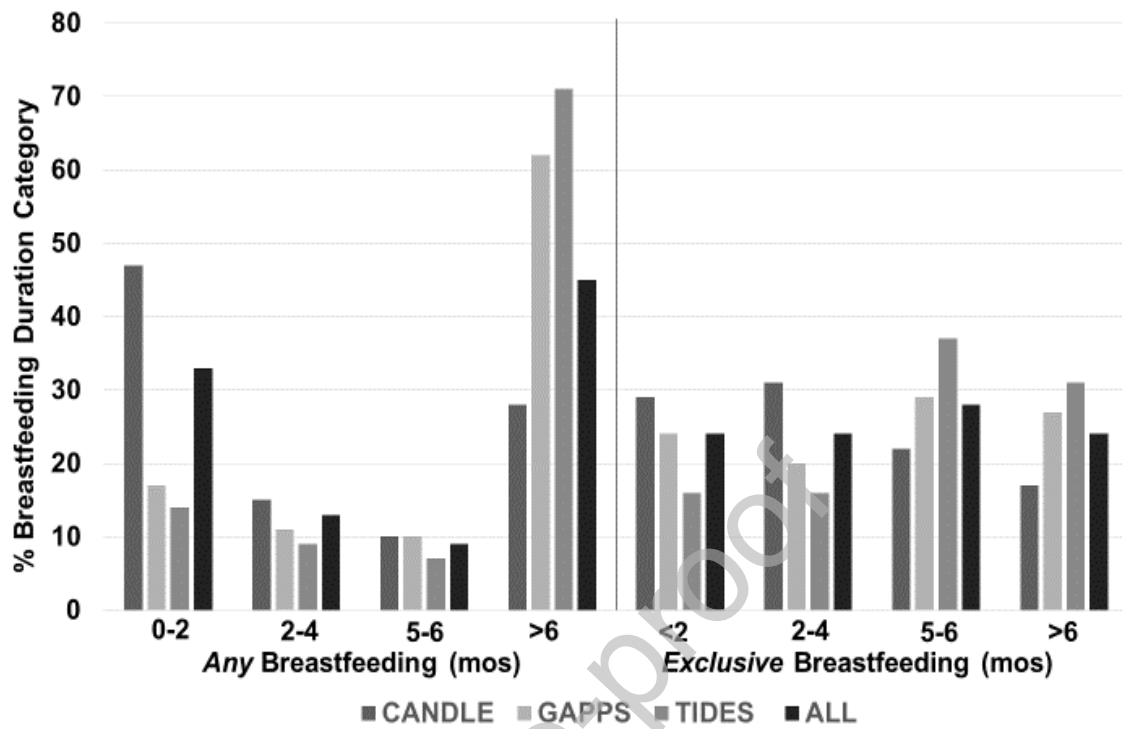


Figure 1. Percentage of *any* and *exclusive* breastfeeding in months (mos) by cohort and for total cohort.

The percentage of children enrolled in PATHWAYS in each breastfeeding duration category for the *any* and *exclusive* breastfeeding exposures.

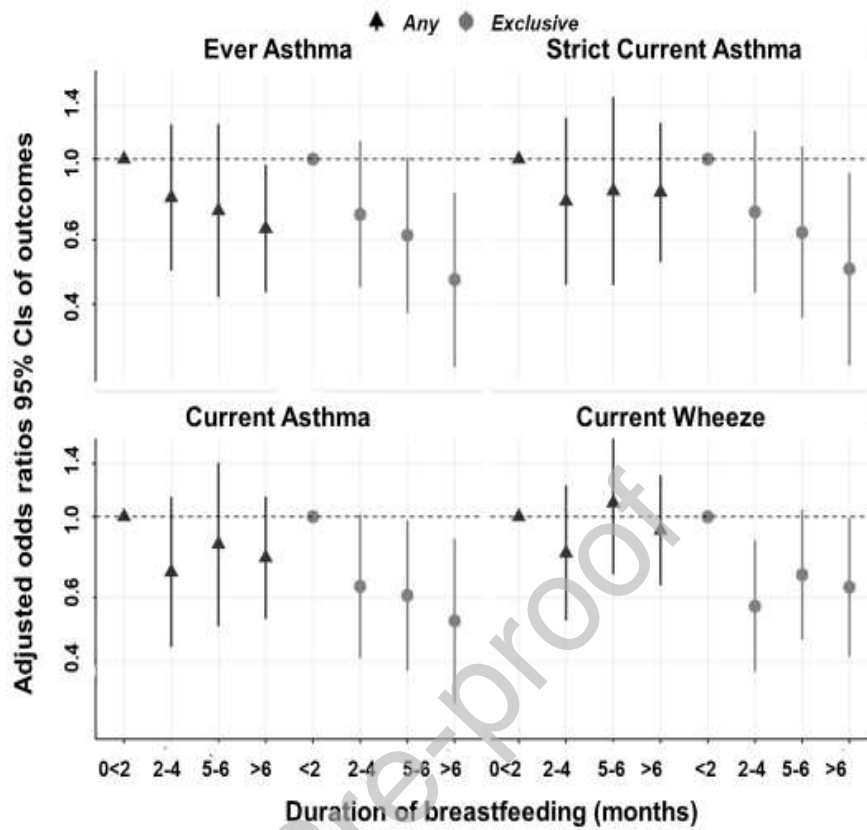


Figure 2. Associations of *any* and *exclusive* breastfeeding with asthma outcomes. Adjusted odds ratios and 95% CIs are graphed in separate models (referent group: none to <2 months [any] or <2months [exclusive]). Covariates: site, maternal age, race, education, asthma, parity, smoking during pregnancy, delivery mode, gestational age, and child sex.