




# Breastfeeding, maternal asthma and wheezing in the first year of life: a longitudinal birth cohort study

Meghan B. Azad <sup>1,2</sup>, Lorena Vehling<sup>1,3</sup>, Zihang Lu<sup>4</sup>, David Dai<sup>5</sup>, Padmaja Subbarao<sup>4</sup>, Allan B. Becker<sup>1,2</sup>, Piushkumar J. Mandhane<sup>6</sup>, Stuart E. Turvey<sup>7</sup>, Diana L. Lefebvre<sup>5</sup> and Malcolm R. Sears<sup>5,8</sup> and the CHILD Study Investigators

**Affiliations:** <sup>1</sup>Dept of Pediatrics and Child Health, University of Manitoba, Winnipeg, MB, Canada. <sup>2</sup>Children's Hospital Research Institute of Manitoba, Winnipeg, MB, Canada. <sup>3</sup>Dept of Community Health Sciences, University of Manitoba, Winnipeg, MB, Canada. <sup>4</sup>Dept of Pediatrics and Physiology, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada. <sup>5</sup>Dept of Medicine, McMaster University, Hamilton, ON, Canada. <sup>6</sup>Dept of Pediatrics, University of Alberta, Edmonton, AB, Canada. <sup>7</sup>Dept of Pediatrics, Child and Family Research Institute and BC Children's Hospital, University of British Columbia, Vancouver, BC, Canada. <sup>8</sup>Canadian Healthy Infant Longitudinal Development Study (investigators listed in acknowledgements).

**Correspondence:** Meghan Azad, Children's Hospital Research Institute of Manitoba, 501G - 715 McDermot Avenue, Winnipeg, Manitoba, Canada R3E 3P4. E-mail: meghan.azad@umanitoba.ca

 @ERSpublications

**When mums with asthma #breastfeed longer, their babies are less likely to wheeze**  
<http://ow.ly/KWEk3089ZEn>

**Cite this article as:** Azad MB, Vehling L, Lu Z, *et al.* Breastfeeding, maternal asthma and wheezing in the first year of life: a longitudinal birth cohort study. *Eur Respir J* 2017; 49: 1602019 [<https://doi.org/10.1183/13993003.02019-2016>].

**ABSTRACT** The impact of breastfeeding on respiratory health is uncertain, particularly when the mother has asthma. We examined the association of breastfeeding and wheezing in the first year of life.

We studied 2773 infants from the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort. Caregivers reported on infant feeding and wheezing episodes at 3, 6 and 12 months. Breastfeeding was classified as exclusive, partial (supplemented with formula or complementary foods) or none.

Overall, 21% of mothers had asthma, 46% breastfed for at least 12 months and 21% of infants experienced wheezing. Among mothers with asthma, breastfeeding was inversely associated with infant wheezing, independent of maternal smoking, education and other risk factors (adjusted rate ratio (aRR) 0.52; 95% CI 0.35–0.77 for  $\geq 12$  versus  $< 6$  months breastfeeding). Compared with no breastfeeding at 6 months, wheezing was reduced by 62% with exclusive breastfeeding (aRR 0.38; 95% CI 0.20–0.71) and by 37% with partial breastfeeding supplemented with complementary foods (aRR 0.63; 95% CI 0.43–0.93); however, breastfeeding was not significantly protective when supplemented with formula (aRR 0.89; 95% CI 0.61–1.30). Associations were not significant in the absence of maternal asthma (*p*-value for interaction  $< 0.01$ ).

Breastfeeding appears to confer protection against wheezing in a dose-dependent manner among infants born to mothers with asthma.

---

This article has supplementary material available from [erj.ersjournals.com](http://erj.ersjournals.com)

Received: Oct 14 2016 | Accepted: Dec 19 2016

Copyright ©ERS 2017

## Introduction

Wheezing is among the most common causes of hospitalisation and healthcare utilisation during infancy [1]. Across different settings, between 20% and 50% of infants experience at least one wheezing episode in the first year of life [2, 3]. Early wheezing is an established risk factor for asthma and chronic obstructive pulmonary disease later in life [4]. While not all wheezing infants will develop persistent respiratory disease, we and others have shown that even transient wheezing during infancy is associated with significantly reduced lung function and increased asthma risk in adolescence [5–7]. Identifying modifiable risk factors and prevention strategies to reduce early wheezing is therefore an important public health priority with significant economic implications.

Breastfeeding may reduce the risk of wheezing by preventing respiratory infections [8], promoting lung growth and development [9], and supporting maturation of the immune system [10]. However, current evidence for these associations is inconsistent [11, 12]. Some studies report protective associations of breastfeeding and wheezing or asthma in early life [13, 14], while others report no association or even an increased risk, particularly when the nursing mother is atopic or asthmatic [15–17]. One study found that breastfeeding effects differed by parental atopy and infant sex [18], although others have failed to confirm this association [19] and most studies have not addressed potential sex differences.

While inconsistencies across studies may be related to differences between study populations, variation in research methods has also contributed to this heterogeneity. Limitations of previous research include recall bias in retrospective studies, imprecise definitions of breastfeeding and inability to adjust for essential confounders [20]. To address these limitations, it has been recommended that studies use a longitudinal design with prenatal recruitment, differentiate between exclusive and total breastfeeding, and minimally adjust for maternal asthma, smoking and socioeconomic status [11]. Following these recommendations, we investigated the association of breastfeeding and wheezing in a pregnancy cohort, including evaluation of dose effects and potential effect modification by maternal asthma and infant sex.

## Methods

### *Study design and population*

We accessed data from the Canadian Healthy Infant Longitudinal Development (CHILD) Study, a population-based birth cohort recruited from four sites in Canada [21]. Women with singleton pregnancies were enrolled between 2009 and 2012 (n=3408) and remained eligible if they delivered a healthy infant >35 weeks gestation (n=3311). For the current analysis, we excluded infants with no wheezing data (n=170), incomplete breastfeeding data (n=210), or missing data for essential covariates (maternal asthma, smoking, education, or ethnicity; n=158), leaving a total of 2773 infants for analysis (84% of the eligible cohort). This sub-cohort did not differ from the full cohort of eligible infants in terms of breastfeeding duration, wheezing or maternal asthma (table S1). This study was approved by the Human Research Ethics Boards at McMaster University and the Universities of Manitoba, Alberta, Toronto and British Columbia.

### *Infant wheezing*

Wheezing in the first year of life was reported by standardised questionnaire at 3, 6 and 12 months of age. Following methods from the International Study of Asthma and Allergies in Children [22], wheezing was defined as “a whistling sound in the chest” lasting for at least 15 min at a time with episodes separated from each other by at least 7 days. We calculated the rate of wheezing as the cumulative number of episodes divided by the total number of follow up months. Most infants (75%) had 12 months of follow up data. Due to missed questionnaires, 11% had 9 months, 9% had 6 months and 5% had 3 months of follow up. For infants with complete wheezing data, we additionally analysed “recurrent wheezing” (two or more episodes) as a dichotomous outcome.

### *Breastfeeding and covariates*

Infant feeding was reported by standardised questionnaire at 3, 6, and 12 months. At 3 months, breastfeeding status was classified as exclusive (human milk only), partial (human milk supplemented with infant formula) or none. At 6 months, partial breastfeeding was sub-classified as “partial with formula” (human milk

---

Support statement: This research was funded by the Heart and Stroke Foundation and Canadian Lung Association Emerging Research Leaders Initiative, in partnership with the Canadian Respiratory Research Network and the Allergy, Genes and Environment Network of Centres of Excellence (AllerGen NCE). The CHILD Study is supported by the Canadian Institutes of Health Research and AllerGen NCE. These entities had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. Funding information for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: None declared.

supplemented with formula, with or without complementary foods) or “partial without formula” (human milk supplemented with complementary foods only). Duration of any breastfeeding was also evaluated (age in months at cessation of breastfeeding) and classified as less than 6 months, 6–12 months, or “12 months” if still breastfeeding at 1 year of age. Infant sex, birth order and maternal age were documented from hospital records. Infant colds were reported by parents and “frequent colds” was defined as four or more colds in the first year. Maternal ethnicity, asthma, education and smoking were self-reported during pregnancy.

### Analysis

Breastfeeding and wheezing prevalence were tabulated against potential confounding variables and univariate associations were examined by Chi-squared test. Poisson regression was used to investigate associations between breastfeeding and wheezing rates, with adjustment for overdispersion based on deviance residuals. Logistic regression was used to investigate the dichotomous outcome of recurrent wheezing. Models were adjusted for recommended covariates (maternal asthma, smoking and education) plus additional potential confounders identified through bivariate screening. Estimated effects are presented as crude and adjusted rate ratios (aRR; for Poisson regression) or odds ratios (aOR; for logistic regression) with 95% confidence intervals. Effect modification by maternal asthma and infant sex was explored through stratification and tested by modelling interaction terms. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

### Role of the funding source

Sponsors had no role in study design, in the collection, analysis and interpretation of data, in the writing of the report or in the decision to submit the paper for publication.

### Results

Among 2773 mother–infant dyads with complete data, the mean $\pm$ SD maternal age was 32.3 $\pm$ 4.6 years and 589 (21%) mothers had asthma. The proportion reporting any breastfeeding was 85% at 3 months, 76% at 6 months and 46% at 12 months (table 1). The rate of exclusive breastfeeding was 59% at 3 months and 18% at 6 months. A total of 1085 wheezing episodes were documented over 29757 months of follow up time, yielding an overall wheezing rate of 0.44 episodes per person–year (95% CI 0.40–0.47). About one in five infants (21%) experienced at least one wheezing episode during the first year of life, and nearly one in ten (9%) experienced recurrent wheezing. The rate and incidence of wheezing was significantly higher among male infants (0.53 episodes per person–year, 25% ever, 11% recurrent) compared to female infants (0.33 episodes per person–year, 17% ever, 7% recurrent) (all  $p < 0.01$ , table 2).

### Maternal and infant factors associated with breastfeeding and wheezing

Several maternal characteristics were associated with both lower rates of breastfeeding and higher rates of infant wheezing, including younger age, lower education, smoking and First Nations’ ethnicity (table 2).

TABLE 1 Breastfeeding and wheezing in the first year of life in the Canadian Healthy Infant Longitudinal Development (CHILD) cohort (n=2773)

	n/N total	%
<b>Breastfeeding at 3 months</b>		
None	407/2773	14.7
Partial	723/2773	26.1
Exclusive	1643/2773	59.2
<b>Breastfeeding at 6 months</b>		
None	642/2742	23.4
Partial (with formula)	722/2742	26.3
Partial (without formula)	886/2742	32.3
Exclusive	492/2742	17.9
<b>Duration of any breastfeeding</b>		
Never	104/2773	3.8
<3 months	303/2773	10.9
3 to <6 months	255/2773	9.2
6 to <12 months	826/2773	29.8
$\geq$ 12 months	1285/2773	46.3
<b>Wheezing in first 12 months</b>		
Any ( $\geq$ 1 episode)	474/2230	21.3
Recurrent ( $\geq$ 2 episodes)	199/2214	9.0

More than half (54%) of mothers over 35 years of age breastfed for at least 12 months, compared with less than a quarter (21%) of mothers under age 25 years. Breastfeeding rates at 12 months were twice as high among mothers with a postgraduate *versus* high school education (60% *versus* 27%) and among non-smoking *versus* smoking mothers (50% *versus* 22%). In parallel with these associations, higher rates of wheezing were observed in infants born to younger mothers (0.85 *versus* 0.39 episodes per person-year for maternal age <25 *versus* >35 years), mothers with lower education (0.73 *versus* 0.31 for high school *versus* postgraduate) and mothers who smoked (0.91 *versus* 0.35 for smoking *versus* non-smoking). Compared with other ethnicities, First Nations' mothers reported the shortest breastfeeding durations and the highest rates of infant wheezing. Infants born before 39 weeks gestational age were less likely to be breastfed at 12 months and more likely to experience wheezing. Similar patterns of association were observed for breastfeeding exclusivity and for recurrent wheezing (table 2). Maternal asthma was a strong risk factor for wheezing (0.86 *versus* 0.32 episodes per person-year for infants with *versus* without maternal asthma) but was not associated with breastfeeding exclusivity or duration.

### **Association of breastfeeding and infant wheezing**

Independent of the aforementioned maternal and infant factors, there was a significant protective and dose-dependent association between breastfeeding and wheezing (table 3). The rate of wheezing was 0.63 episodes per person-year among those breastfed for less than 6 months, 0.50 among those breastfed for 6 to <12 months and 0.31 among those breastfed for 12 months or more. After adjusting for maternal age, asthma, ethnicity, smoking, education, study site, infant sex and gestational age, there was a 33% reduced rate of wheezing among infants breastfed for 12 months or more (aRR 0.67, 95% CI 0.55–0.81) compared with those breastfed for less than 6 months. There was also a dose response according to breastfeeding exclusivity: compared with no breastfeeding at 3 months, there was a 14% reduced rate of wheezing with partial breastfeeding (aRR 0.86, 95% CI 0.69–1.07) and a 26% reduced rate of wheezing with exclusive breastfeeding (aRR 0.74; 95% CI 0.60–0.91). Exclusive breastfeeding at 6 months was similarly protective (aRR 0.64; 95% CI 0.49–0.84). Sub-classification of partial breastfeeding revealed that supplementation with formula attenuated this association (aRR 0.94; 95% CI 0.77–1.15) whereas it remained significant following supplementation with complementary food without formula (aRR 0.77; 95% CI 0.63–0.94).

Similar dose-dependent patterns of association were observed for the incidence of recurrent wheezing (table S2). Adjustment for frequent colds did not attenuate the observed associations (table S3).

### **Effect modification by maternal asthma and infant sex**

In stratified analyses, the inverse association of breastfeeding and wheezing was confined to infants whose mothers had asthma (figure 1, table 4). For example, among infants with maternal asthma, the rate of wheezing was reduced from 1.40 to 0.33 episodes per person-year with 6 months exclusive breastfeeding (aRR 0.38, 95% CI 0.20–0.71) whereas no significant association was observed among infants without maternal asthma (0.39 *versus* 0.27 episodes per person-year; aRR 0.92, 95% CI 0.68–1.23) (p-value for interaction 0.001). Similar evidence of effect modification was found for breastfeeding exclusivity at 3 months and total breastfeeding duration (p-value interaction 0.008 and 0.004, respectively). Further stratification by infant sex revealed somewhat stronger associations among male infants (figure S1, table S4), although interactions by sex did not reach statistical significance (p=0.08 for breastfeeding exclusivity at 3 months; p=0.09 for breastfeeding duration). Overall, the highest wheezing rates were observed among males with maternal asthma (2.02 episodes per person-year among those breastfed less than 3 months) and these infants appeared to benefit the most from higher breastfeeding exclusivity and duration (0.35 episodes per person-year with 6 months exclusive breastfeeding; aRR 0.32; 95% CI 0.12–0.83).

## **Discussion**

In the prospective CHILD pregnancy cohort, we found evidence of a strong protective association between breastfeeding and wheezing in the first year of life, particularly among infants born to mothers with asthma. This association was dose-dependent (stronger with longer or more exclusive breastfeeding), independent of established risk factors for infant wheezing and early breastfeeding cessation, and was especially evident in male infants.

Our results confirm and extend previous research on breastfeeding and infant wheezing. In the cross-sectional International Study of Wheezing in Infants, breastfeeding for at least 3 months was associated with a reduced odds of recurrent wheezing in the first year of life (OR 0.79, 95% CI 0.72–0.87) [2]. In the prospective Western Australian Pregnancy Cohort Study, there was an increased risk of wheezing illness in the first year when cow's milk was introduced before 6 months (OR 2.07; 95% CI 1.47–2.90) [23]. In a recent meta-analysis by DOGARU *et al.* [11], "more *versus* less breastfeeding" was associated with a 30% reduced risk of wheezing in the first two years of life (pooled OR 0.70, 95% CI 0.65–0.76, 28 studies, I<sup>2</sup>=64%). Studies included in this review were highly heterogeneous in their definitions of breastfeeding and

TABLE 2 Prevalence and associations of potential confounders with breastfeeding and infant wheezing in the Canadian Healthy Infant Longitudinal Development (CHILD) cohort (n=2773)

	Prevalence (n=2773)		Exclusive breastfeeding at 3 months (n=2773)		Any breastfeeding at 1 year (n=2773)		Recurrent wheezing in first year (n=2214)		Wheezing rate in first year (n=2773)	
	n (%)	n (%)	p-value <sup>#</sup>	n (%)	p-value <sup>#</sup>	n (%)	p-value <sup>#</sup>	Episodes per person-year	p <sup>¶</sup>	
<b>Overall</b>		1643 (59.3)		1285 (46.3)		199 (9.0)		0.44		
<b>Study site</b>										
Edmonton	639 (23.0)	347 (54.3)	***	242 (37.9)	***	50 (10.4)	*	0.48	***	
Toronto	631 (22.8)	354 (56.1)		269 (42.6)		43 (9.5)		0.41		
Vancouver	642 (23.2)	446 (69.5)		409 (63.7)		30 (5.7)		0.27		
Winnipeg	861 (31.1)	496 (57.6)		365 (42.4)		76 (10.1)		0.55		
<b>Maternal asthma</b>										
No	2184 (78.8)	1304 (59.7)		1007 (46.1)		122 (7.0)	***	0.32	***	
Yes	589 (21.2)	339 (57.6)		278 (47.2)		77 (16.0)		0.86		
<b>Prenatal smoke exposure</b>										
Mother smokes	241 (8.7)	90 (37.3)	***	52 (21.6)	***	31 (18.3)	***	0.90	***	
Other smoker in home	329 (11.9)	170 (51.7)		137 (41.6)		36 (13.5)		0.70		
None	2203 (79.4)	1383 (62.8)		1096 (49.8)		132 (7.4)		0.35		
<b>Maternal education</b>										
High school or below	235 (8.5)	102 (43.4)	***	63 (26.8)	***	24 (13.6)	*	0.73	***	
Some postsecondary	400 (14.4)	214 (53.5)		160 (40.0)		36 (11.9)		0.50		
Completed postsecondary	1615 (58.2)	970 (60.1)		750 (46.4)		111 (8.4)		0.42		
Postgraduate degree	523 (18.9)	357 (68.3)		312 (59.7)		28 (6.7)		0.31		
<b>Maternal ethnicity</b>										
Asian	422 (15.2)	247 (58.5)	**	226 (53.6)	**	14 (4.3)	***	0.22	***	
Caucasian	2064 (74.4)	1253 (60.7)		933 (45.2)		142 (8.5)		0.42		
First Nations	114 (4.1)	56 (49.1)		44 (38.6)		25 (32.5)		1.38		
Other	173 (6.2)	87 (50.3)		82 (47.4)		18 (14.0)		0.59		
<b>Maternal age years</b>										
<25	184 (6.6)	64 (34.8)	***	38 (20.7)	***	27 (19.9)	***	0.85	***	
25 to <30	628 (22.7)	384 (61.2)		244 (38.9)		45 (8.7)		0.57		
30 to <35	1177 (42.5)	715 (60.8)		581 (49.4)		71 (7.6)		0.34		
≥35	784 (28.3)	480 (61.2)		422 (53.8)		56 (9.0)		0.39		
<b>Infant sex</b>										
Female	1308 (47.2)	813 (62.2)	**	618 (47.3)		72 (7.1)	**	0.33	***	
Male	1465 (52.8)	830 (56.7)		667 (45.5)		127 (10.7)		0.53		
<b>Birth order</b>										
First born	1528 (55.1)	886 (58.0)		703 (46.0)		87 (7.0)	***	0.37	***	
Not first born	1245 (44.9)	757 (60.8)		582 (46.8)		112 (11.4)		0.52		
<b>Birth mode</b>										
Vaginal	2077 (75.0)	1267 (61.0)	***	994 (47.9)	**	153 (9.1)		0.43		
Caesarean	693 (25.0)	375 (54.1)		290 (41.9)		46 (8.6)		0.45		
<b>Gestational age weeks</b>										
34–37	286 (10.3)	145 (50.7)	***	111 (38.8)	***	26 (11.3)	*	0.65	***	
38	471 (17.0)	244 (51.8)		188 (39.9)		43 (11.6)		0.50		
≥39	2016 (72.7)	1254 (62.2)		986 (48.9)		130 (8.1)		0.39		

<sup>#</sup>: Chi-squared test comparison; <sup>¶</sup>: Poisson regression comparison; \*: p<0.05; \*\*: p<0.01; \*\*\*: p<0.001.

wheezing, and the majority did not meet recommended criteria for breastfeeding research [20] such as nonreliance on prolonged recall, sufficient duration of breastfeeding, assessment of dose-effects and adjustment for essential confounders. Our study addressed these criteria by prospectively collecting feeding data at three time points in the first year of life, examining dose effects according to breastfeeding duration, exclusivity and extent of supplementation, and controlling for recommended covariates (maternal asthma, smoking and education) plus additional confounders identified through bivariate screening (gestational age, maternal age and ethnicity).

A previous study reported that breastfeeding may have diminished benefits or even detrimental effects in children breastfed by asthmatic mothers [16]. We did not find evidence of this in our cohort, although we

TABLE 3 Associations of breastfeeding and wheezing rates in the first year of life in the Canadian Healthy Infant Longitudinal Development (CHILD) cohort (n=2773)

Breastfeeding measure	n	Wheezing episodes	Months of follow up	Wheezing rate (episodes per person-year)	Crude RR (95% CI)	Adjusted <sup>#</sup> RR (95% CI)
<b>Breastfeeding at 3 months</b>						
None	407	232	4044	0.69	1.00 (reference)	1.00 (reference)
Partial (with formula)	723	305	7764	0.47	0.68 (0.55–0.86)	0.86 (0.69–1.07)
Exclusive	1643	548	17949	0.37	0.53 (0.43–0.65)	0.74 (0.60–0.91)
<b>Breastfeeding at 6 months</b>						
None	642	340	6564	0.62	1.00 (reference)	1.00 (reference)
Partial (with formula)	722	303	7863	0.46	0.74 (0.61–0.91)	0.94 (0.77–1.15)
Partial (without formula)	886	300	9885	0.36	0.59 (0.48–0.72)	0.77 (0.63–0.94)
Exclusive	492	123	5289	0.28	0.45 (0.34–0.59)	0.64 (0.49–0.84)
<b>Breastfeeding duration<sup>¶</sup></b>						
<6 months	662	348	6654	0.63	1.00 (reference)	1.00 (reference)
6 to <12 months	826	370	8958	0.50	0.79 (0.65–0.96)	0.99 (0.82–1.20)
≥12 months	1285	367	14 145	0.31	0.50 (0.41–0.60)	0.67 (0.55–0.81)

<sup>#</sup>: Adjusted for study site, maternal age, ethnicity, asthma, smoking during pregnancy, postsecondary education, infant sex and gestational age; <sup>¶</sup>: refers to any breastfeeding. Associations determined by Poisson regression per person-year.

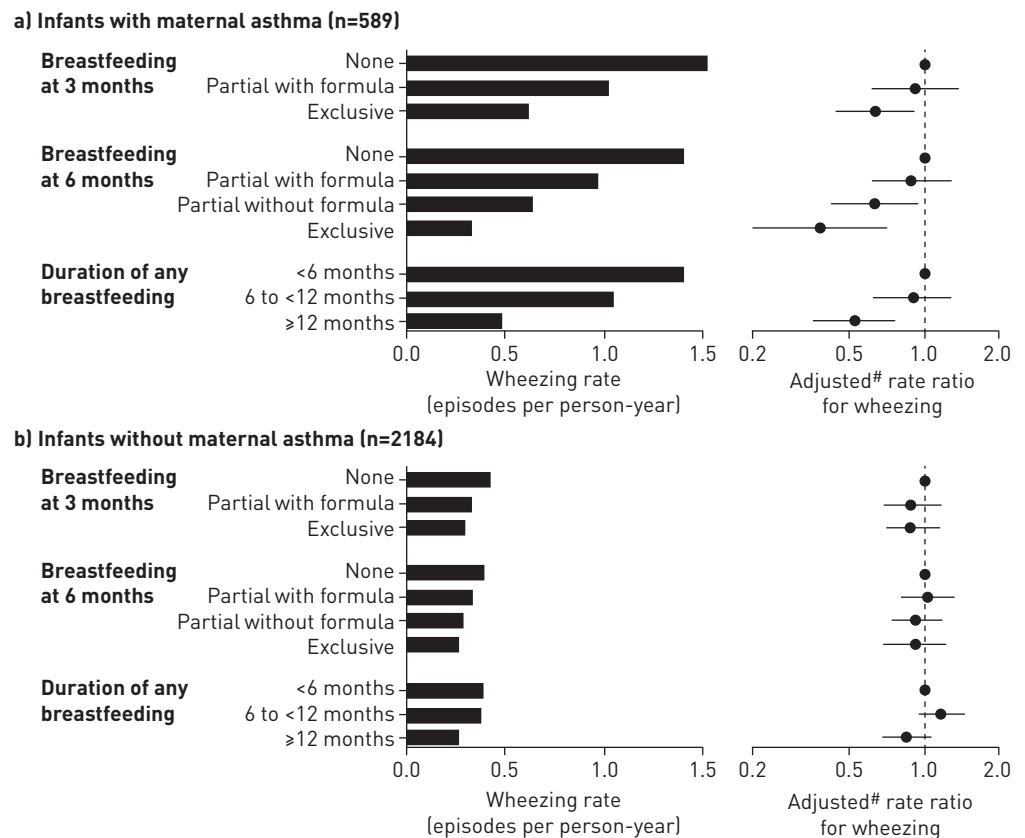


FIGURE 1 Breastfeeding and wheezing rates in the first year of life in the Canadian Healthy Infant Longitudinal Development (CHILD) Study, for a) infants with maternal asthma (n=589) and b) infants without maternal asthma (n=2184). Among infants born to mothers with asthma, wheezing rates are progressively lower with increasing breastfeeding exclusivity and duration. <sup>#</sup>: rate ratios were adjusted for study site; maternal age, postsecondary education, ethnicity, smoking during pregnancy; infant sex and gestational age.

TABLE 4 Associations of breastfeeding and wheezing rates in the first year of life in the Canadian Healthy Infant Longitudinal Development (CHILD) cohort, stratified by maternal asthma (n=2773)

Breastfeeding measure	Maternal asthma (n=589)		No maternal asthma (n=2184)		p for effect modification*
	Wheezing rate (episodes per person-year)	Adjusted <sup>#</sup> RR (95%CI)	Wheezing rate (episodes per person-year)	Adjusted <sup>#</sup> RR (95%CI)	
<b>Breastfeeding at 3 months</b>					
None	1.52	1.00 (reference)	0.43	1.00 (reference)	0.008
Partial (with formula)	1.02	0.92 (0.61–1.38)	0.33	0.89 (0.68–1.18)	
Exclusive	0.62	0.63 (0.43–0.93)	0.30	0.89 (0.69–1.15)	
<b>Breastfeeding at 6 months</b>					
None	1.40	1.00 (reference)	0.39	1.00 (reference)	0.001
Partial (with formula)	0.97	0.89 (0.61–1.30)	0.33	1.03 (0.80–1.32)	
Partial (without formula)	0.64	0.63 (0.42–0.94)	0.29	0.93 (0.73–1.19)	
Exclusive	0.33	0.38 (0.20–0.71)	0.27	0.92 (0.68–1.23)	
<b>Breastfeeding duration<sup>¶</sup></b>					
<6 months	1.41	1.00 (reference)	0.39	1.00 (reference)	0.004
6 to <12 months	1.05	0.90 (0.62–1.29)	0.37	1.17 (0.93–1.47)	
≥12 months	0.49	0.52 (0.35–0.77)	0.26	0.84 (0.67–1.07)	

<sup>#</sup>: Adjusted for study site, maternal age, ethnicity, smoking during pregnancy, postsecondary education, infant sex and gestational age; <sup>¶</sup>: refers to any breastfeeding. Associations determined by Poisson regression.\*: Determined by modelling an interaction term.

studied a much younger population. In our study of infants, breastfeeding was more protective among mothers with asthma. For example, breastfeeding for ≥12 months was significantly protective in infants born to mothers with asthma (aRR 0.52) whereas the association was tempered and non-significant in those born to mothers without asthma (aRR 0.84). These findings are consistent with a report by DOGARU *et al.* [24] that breastfeeding was associated with improved lung function by school age, especially in children of mothers with asthma. Together, these results suggest that all mothers, regardless of their own respiratory health, can promote optimal lung development in their infants through breastfeeding.

Interestingly, we found that breastfeeding tended to be more protective against wheezing in male infants. Male sex is a well-known risk factor for infant wheezing, yet to our knowledge, no previous studies have reported sex-stratified analyses of breastfeeding and wheezing during infancy, although sex differences in breastfeeding effects have been reported in other contexts. For example, ODDY *et al.* [25] found that breastfeeding was positively associated with academic achievement in boys only, and sex differences in the association of breastfeeding and infant growth have also been reported [26]. It has been hypothesised that female sex hormones in breast milk may account for sex differences in breastfeeding effects, since male and female infants differ in their biological responses to sex hormones [18]. Regardless of the underlying mechanisms, which warrant further investigation, our results highlight the importance of considering sex differences in breastfeeding research, and suggest that previous studies could have missed or under-estimated effects in males.

Another unique aspect of our study is the detailed analysis of breastfeeding intensity and duration. Many previous studies have simply dichotomised breastfeeding (any or none) at a single time point, whereas we classified breastfeeding exclusivity (exclusive, partial or none) at two time points and further evaluated total breastfeeding duration. We observed increasing protection with increasing breastfeeding exclusivity in the first 6 months of life, and added protection from longer breastfeeding duration. While our study is observational and cannot prove causation, this apparent dose response provides support for a causal association, suggesting that policies to support breastfeeding could have a positive impact on infant respiratory health at the population level. Moreover, our findings identify specific subgroups that may especially benefit from targeted interventions to increase breastfeeding exclusivity and duration, including younger mothers, mothers who smoke, and mothers with lower education.

Our findings also contribute new evidence regarding the introduction of complementary foods. The World Health Organization currently recommends exclusive breastfeeding for 6 months to achieve optimal infant growth and development [27], yet there is emerging evidence that earlier introduction of certain complementary foods may reduce the risk of allergic disease [28]. We sub-categorized “partial breastfeeding”

at 6 months to separately address the impact of introducing formula *versus* complementary foods – an important distinction that is rarely reported. We observed significant protective associations for exclusive breastfeeding and partial breastfeeding supplemented with complementary foods, whereas the association for partial breastfeeding supplemented with formula was not significant. These results suggest that the increased risk of infant wheezing observed with non-exclusive breastfeeding is likely explained by the substitution of human milk with infant formula, rather than addition of complementary foods. This finding has important practical implications for infant feeding recommendations, particularly given the ongoing debate regarding the potential benefits of earlier introduction to complementary foods for allergy prevention [29].

To address the possibility that breastfeeding reduces infant wheezing primarily by preventing respiratory infections, we adjusted our analyses for frequent colds. This did not significantly change the observed associations, suggesting that breastfeeding confers protection against non-infectious wheezing, which is a strong risk factor for subsequent asthma development [30]. In addition to directly transmitting protective maternal antibodies, human milk provides a multitude of bioactive constituents that nourish gut microbiota and support lung growth [8–10], providing additional mechanisms to prevent wheezing and promote healthy lung development.

The strengths of our study include the frequent prospective documentation of infant feeding and wheezing in a large nationally-representative cohort; adjustment for key confounders including maternal asthma, smoking and education; assessment of dose effects; and the investigation of sex differences and effect modification by maternal asthma. The use of parent report to identify wheezing is a limitation, although we used an internationally-validated questionnaire [22]. We cannot exclude the possibility of residual confounding in our observational study, although we have controlled for essential confounders identified in previous studies plus additional confounders identified in our own analysis. Finally, our follow up was limited to 1 year; however, multiple studies have shown that wheezing during this critical period predicts long-term respiratory health [5–7]. Still, extended follow-up will be important since other cohorts have reported time-dependent associations with discrepant results for the impact of breastfeeding on wheezing during infancy *versus* later in childhood [16]. Further follow up of the CHILD cohort is underway, including pulmonary function testing and formal asthma diagnosis at 5 years of age. These assessments will facilitate extended evaluation of the association between breastfeeding and respiratory health.

### Conclusion

Our results strengthen the existing evidence that breastfeeding confers protection against wheezing in early life, and further identify novel features of this association. We observed stronger protection from longer and more exclusive breastfeeding, primarily in infants with maternal history of asthma, and especially in males. The benefits of exclusive breastfeeding were diminished by supplementation with infant formula before 6 months, but not by the introduction of complementary foods. These findings provide new evidence to inform infant feeding guidelines and guide further research on the bioactive properties of human milk. Given the substantial health and economic burden imposed by infant wheezing and the potential for persistent respiratory morbidity, our results support the endorsement of breastfeeding as a cost-effective strategy to prevent infant wheezing and promote lifelong respiratory health.

### Acknowledgements

We are grateful to all the families who took part in this study, and the whole CHILD team, which includes interviewers, nurses, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, and receptionists. We also thank Amy Dytnerki for assistance with the literature review for this manuscript, and Atul Sharma and Arthur Owora for their statistical expertise.

CHILD investigators include: M.R. Sears (Director), McMaster University; P. Subbarao P (co-Director), The Hospital for Sick Children; S.S. Anand, McMaster University; M.B. Azad, University of Manitoba; A.B. Becker, University of Manitoba; A.D. Befus, University of Alberta; M. Brauer, University of British Columbia; J.R. Brook, University of Toronto; E. Chen, Northwestern University, Chicago; M. Cyr, McMaster University; D. Daley, University of British Columbia; S. Dell, Sick Children's Hospital; J.A. Denburg, McMaster University; Q. Duan, Queen's University; T. Eiwegger, The Hospital for Sick Children; H. Grasemann, Sick Children's Hospital; K. HayGlass, University of Manitoba; R. Hegele, Sick Children's Hospital; D.L. Holness, University of Toronto; P. Hystad, University of Oregon; W.Y.W. Lou, University of Toronto; M.S. Kobor, University of British Columbia; T.R. Kollman, University of British Columbia; A.L. Kozyrskyj, University of Alberta; C. Laprise, Université du Québec à Chicoutimi; J. Macri, McMaster University; P.M. Mandhane, University of Alberta; G. Miller, Northwestern University, Chicago; T. Moraes, Sick Children's Hospital; P.D. Paré, University of British Columbia; C. Ramsey, University of Manitoba; F. Ratjen, Sick Children's Hospital; A. Sandford, University of British Columbia; J.A. Scott, University of Toronto; J. Scott, University of Toronto; F. Silverman, University of Toronto; E. Simons, University of Manitoba; T. Takaro, Simon Fraser University; S. Tebbutt, University of British Columbia; T. To, Sick Children's Hospital; S.E. Turvey, University of British Columbia.

### References

- 1 El-Gamal YM, El-Sayed SS. Wheezing in infancy. *World Allergy Organ J* 2011; 4: 85–90.



- 2 Garcia-Marcos L, Mallol J, Sole D, *et al.* International study of wheezing in infants: risk factors in affluent and non-affluent countries during the first year of life. *Pediatr Allergy Immunol* 2010; 21: 878–888.
- 3 Kuehni CE, Strippoli MP, Low N, *et al.* Wheeze and asthma prevalence and related health-service use in white and south Asian pre-schoolchildren in the United Kingdom. *Clin Exp Allergy* 2007; 37: 1738–1746.
- 4 Tagiyeva N, Devereux G, Fielding S, *et al.* Outcomes of Childhood Asthma and Wheezy Bronchitis. A 50-Year Cohort Study. *Am J Respir Crit Care Med* 2016; 193: 23–30.
- 5 Henderson J, Granell R, Heron J, *et al.* Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008; 63: 974–980.
- 6 Morgan WJ, Stern DA, Sherrill DL, *et al.* Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005; 172: 1253–1258.
- 7 Azad MB, Chan-Yeung M, Chan ES, *et al.* Wheezing patterns in early childhood and the risk of respiratory and allergic disease in adolescence. *JAMA Pediatr* 2016; 170: 393–395.
- 8 Victora CG, Bahl R, Barros AJ, *et al.* Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet* 2016; 387: 475–490.
- 9 Waidyatillake NT, Allen KJ, Lodge CJ, *et al.* The impact of breastfeeding on lung development and function: a systematic review. *Expert Rev Clin Immunol* 2013; 9: 1253–1265.
- 10 Turfkruyer M, Verhasselt V. Breast milk and its impact on maturation of the neonatal immune system. *Curr Opin Infect Dis* 2015; 28: 199–206.
- 11 Dogaru CM, Nyffenegger D, Pescatore AM, *et al.* Breastfeeding and childhood asthma: systematic review and meta-analysis. *Am J Epidemiol* 2014; 179: 1153–1167.
- 12 Lodge CJ, Tan DJ, Lau MX, *et al.* Breastfeeding and asthma and allergies: a systematic review and meta-analysis. *Acta Paediatr* 2015; 104: 38–53.
- 13 Dell S, To T. Breastfeeding and asthma in young children: findings from a population-based study. *Arch Pediatr Adolesc Med* 2001; 155: 1261–1265.
- 14 Kull I, Almqvist C, Lilja G, *et al.* Breast-feeding reduces the risk of asthma during the first 4 years of life. *J Allergy Clin Immunol* 2004; 114: 755–760.
- 15 Burgess SW, Dakin CJ, O’Callaghan MJ. Breastfeeding does not increase the risk of asthma at 14 years. *Pediatrics* 2006; 117: e787–e792.
- 16 Wright AL, Holberg CJ, Taussig LM, *et al.* Factors influencing the relation of infant feeding to asthma and recurrent wheeze in childhood. *Thorax* 2001; 56: 192–197.
- 17 Sears MR, Greene JM, Willan AR, *et al.* Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. *Lancet* 2002; 360: 901–907.
- 18 Mandhane PJ, Greene JM, Sears MR. Interactions between breast-feeding specific parental atopy, and sex on development of asthma and atopy. *J Allergy Clin Immunol* 2007; 119: 1359–1366.
- 19 Elliott L, Henderson J, Northstone K, *et al.* Prospective study of breast-feeding in relation to wheeze, atopy, and bronchial hyperresponsiveness in the Avon Longitudinal Study of Parents and Children (ALSPAC). *J Allergy Clin Immunol* 2008; 122: 49–54.
- 20 Kramer MS. Does breast feeding help protect against atopic disease? Biology, methodology, and a golden jubilee of controversy. *J Pediatr* 1988; 112: 181–190.
- 21 Subbarao P, Anand SS, Becker AB, *et al.* The Canadian Healthy Infant Longitudinal Development (CHILD) Study: examining developmental origins of allergy and asthma. *Thorax* 2015; 70: 998–1000.
- 22 Asher MI, Keil U, Anderson HR, *et al.* International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8: 483–491.
- 23 Oddy WH, Sly PD, de Klerk NH, *et al.* Breast feeding and respiratory morbidity in infancy: a birth cohort study. *Arch Dis Child* 2003; 88: 224–228.
- 24 Dogaru CM, Strippoli MP, Spycher BD, *et al.* Breastfeeding and lung function at school age: does maternal asthma modify the effect? *Am J Respir Crit Care Med* 2012; 185: 874–880.
- 25 Oddy WH, Li J, Whitehouse AJ, *et al.* Breastfeeding duration and academic achievement at 10 years. *Pediatrics* 2011; 127: e137–e145.
- 26 Nagahara K, Dobashi K, Itabashi K. Feeding choice has a gender-associated effect on infant growth. *Pediatr Int* 2013; 55: 481–487.
- 27 World Health Organization. Global strategy on infant and young child feeding. WHO, Geneva, 2002.
- 28 Perkin MR, Logan K, Tseng A, *et al.* Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med* 2016; 374: 1733–1743.
- 29 Abrams EM, Becker AB. Food introduction and allergy prevention in infants. *CMAJ* 2015; 187: 1297–1301.
- 30 Pescatore AM, Dogaru CM, Duembgen L, *et al.* A simple asthma prediction tool for preschool children with wheeze or cough. *J Allergy Clin Immunol* 2014; 133: 111–118 e1-13.