

Original Article

The interplay between eczema and breastfeeding practices may hide breastfeeding's protective effect on childhood asthma

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What is already known about this topic? Longer duration of breastfeeding may be protective against asthma; however, early allergic disease such as eczema may influence a mother's breastfeeding practices, which may bias observable associations.

What does this article add to our knowledge? Increased duration of breastfeeding was associated with a modest reduction in odds of asthma among children without eczema in the first year of life; this association was masked before stratification by eczema in infancy.

How does this study impact current management guidelines? Future studies examining breastfeeding practices and the risk of allergic outcomes in later childhood need to consider the presence of early-life allergic manifestations and possible disease-related modification of exposure.

BACKGROUND: Longer duration of breastfeeding may be protective against asthma. However, early manifestations of allergic disease, such as eczema, are risk factors for asthma and can influence the duration of breastfeeding, and hence, may bias observable associations.

OBJECTIVE: To examine the relationship between breastfeeding ever and duration and the development of asthma and allergic asthma phenotypes, stratified by a diagnosis of eczema during or after the breastfeeding period.

METHODS: A total of 3663 children participated in the 6-year-old follow-up of the HealthNuts study, a population-based, longitudinal study of allergic diseases in Australia. At age 1 year, breastfeeding and eczema data were collected and at age 6 years, information on wheeze, medication use, and parental report of doctor-diagnosed asthma were obtained, both via questionnaire. Skin prick test responses to food and aeroallergens at age 6 years further distinguished asthmatic children into allergic and nonallergic phenotypes.

RESULTS: Breastfeeding initiation was not associated with current asthma at age 6 years (adjusted odds ratio, 0.76; 95% CI, 0.45-1.29) when compared with never breastfeeding. Results were similar for length of exclusiveness and overall duration of breastfeeding, and allergic and nonallergic asthma phenotypes. However, increased duration of breastfeeding among children without eczema in infancy was associated with reduced odds of asthma (per month increase, adjusted odds ratio, 0.98; 95% CI, 0.95-1.0; $P = .05$), which equates to 0.86 (95% CI, 0.74-1.0) reduced odds of asthma for a 6-month increase in breastfeeding. This association was not apparent in children who were diagnosed with eczema during breastfeeding (adjusted odds ratio, 1.03; 95% CI, 0.98-1.08; $P = .3$).

CONCLUSIONS: Longer duration of breastfeeding was associated with a reduced odds of asthma among children without eczema in the first year of life; this association was masked before stratification by eczema in infancy. Future studies examining breastfeeding practices and the risk of allergic outcomes in later

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Abbreviations used*aOR*-Adjusted odds ratio*RTI*-Respiratory tract infection*SPT*-Skin prick test

childhood need to consider the presence of early-life allergic manifestations impacting on breastfeeding behavior. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Breastfeeding; Asthma; Asthma phenotypes; Eczema; Allergy; Sensitization

INTRODUCTION

Breastfeeding is widely regarded as the optimal form of infant feeding. As well as reducing respiratory and gastrointestinal infections in infancy,¹ breastfeeding is reported to improve numerous health outcomes into adulthood.² Despite these benefits, the influence of breastfeeding on asthma prevalence in childhood is less clear and findings within the literature remain inconsistent.

Previous studies investigating this relationship have illustrated a protective effect,³⁻¹⁰ no effect,¹¹⁻¹⁵ or even an increased risk of asthma with prolonged duration of breastfeeding.^{16,17} Although the most recent meta-analysis of 42 articles demonstrated an overall modest protective effect (pooled odds ratio, 0.88; 95% CI, 0.82-0.95), the authors acknowledged the low-quality nature of this result given substantial heterogeneity between studies.¹⁸ There has only been 1 randomized controlled trial assessing breastfeeding practices and the risk of allergic and respiratory outcomes. The intervention, which promoted prolonged and exclusive breastfeeding in Belarus, showed no protective effect on atopic eczema or asthma.¹⁹ However, this finding may not be directly applicable to Westernized countries where both breastfeeding and allergy rates are high. Randomized controlled trials of randomizing individual children to breastfeeding exposures are not feasible to conduct for ethical and logistical reasons, necessitating the use of observational studies to examine these relationships.

There is considerable overlap between allergic diseases in childhood, and few studies have explicitly addressed the potential for early-life signs of allergic disease to impact on breastfeeding practices. Infantile eczema is a known risk factor for asthma, and both eczema and asthma are manifestations of the allergic disease diathesis.²⁰ Early signs of eczema in infants increased the likelihood of a mother breastfeeding for longer, possibly in the hope that it will prevent the development of other allergic diseases or reduce the severity of eczema.²¹ Failure to adequately account for this association may lead to an attenuation of observable protective associations between breastfeeding and asthma or spurious associations suggesting an increased risk in those who are breast-fed for longer because of early eczema.

In addition, given that allergic asthma and non-allergic asthma phenotypes are known to have distinct risk factors, distinguishing between the effects of breastfeeding on both phenotypes is important in the establishment of targeted prevention.^{22,23} Only a select number of studies have stratified results on the basis of asthma phenotypes, and only 1 controlled for the presence of

early-life allergic disease, with results being quite mixed.^{6,8,9} Therefore, we aimed to investigate the relationship between breastfeeding ever and duration and the development of asthma and allergic asthma phenotypes at age 6 years, stratified by the presence of eczema during or after the breastfeeding period, using prospective data collected from a population-based, longitudinal study of allergy and asthma.

METHODS

Study design

Recruitment. HealthNuts is a population-based, longitudinal cohort study of allergic diseases including asthma undertaken in Melbourne, Australia. In brief, infants aged 11 to 15 months whose parents/guardians could read and understand English were eligible and invited to participate from 170 council-run immunization sessions across Melbourne (n = 5276 [74% participation]).²⁴ Parents or guardians completed a questionnaire that included questions on breastfeeding duration and length of exclusiveness, as well as other information regarding common childhood conditions (including whether a doctor had diagnosed eczema and the month of diagnosis), environmental exposures, and family history of allergic diseases. Infants also underwent skin prick test (SPT) to 4 common food allergens and were invited for oral food challenge if a detectable wheal was observed (described in detail previously).²⁵

Age 6-year follow-up. At age 6 years, all parents were mailed a full questionnaire collecting information about their child's asthma and allergy status, ongoing feeding practices, and environmental exposures. Children were also invited to participate in a health assessment that included SPT.²⁶ If parents did not respond after reminders, they were invited to complete a short 5-minute telephone questionnaire obtaining key information regarding their child's current asthma status.

Skin prick tests. At ages 1 and 6 years, SPTs were administered using a single-time lancet (Stallergenes, Antony, France) on the child's back using allergen extracts (ALK-Abello, Madrid, Spain) along with a positive control (10 mg/mL histamine) and a negative control (saline). At age 1 year, SPT was conducted to peanut, hen's egg, sesame, and either cow's milk or shrimp. At age 6 years, SPT was conducted to peanut, egg, sesame, soy, almond, cashew, hazelnut, shellfish, cow's milk, wheat, house-dust mite, rye grass, Bermuda grass, cat hair, alternaria, birch mix, cladosporium, and dog hair.

Definitions of exposure and outcome variables

Breastfeeding. Questionnaires administered at age 12 months captured the age of breastfeeding initiation and cessation in months. Children were categorized as never or ever breast-fed. Of those ever breast-fed, exclusive breastfeeding was defined as breastfeeding without the addition of any formula, or solid foods and was categorized as never, less than 6 months, or greater than 6 months. Overall duration was the total length of breastfeeding, regardless of exclusivity, and was treated as both a continuous (per month) and categorical variable (<3 months, 3 to <6 months, 6 to <12 months, or >12 months).

Eczema. Eczema was defined as a parent report of a doctor diagnosis of eczema in the first year of life and was further categorized by the age of diagnosis into no eczema, eczema diagnosed

during breastfeeding, and eczema diagnosed after the cessation of breastfeeding.

Asthma. Data on asthma were collected via parental questionnaire at age 6 years, including questions taken from the validated International Study of Asthma and Allergies in Childhood questionnaire.²⁷ Current asthma was defined as parental report of doctor-diagnosed asthma plus either wheeze or use of common asthma medication (relievers and preventers) in the previous 12 months. Wheezing in the first year of life (which was considered as a covariate not outcome) was captured in the recruitment questionnaire at age 12 months.

Atopic sensitization and asthma phenotypes. Atopic sensitization was defined as a positive SPT result (≥ 3 mm wheal) to 1 or more food or aeroallergens at age 6 years. Asthma phenotypes were defined as allergic asthma (current asthma in the presence of sensitization) and nonallergic asthma (current asthma without sensitization,) with children without asthma as the reference group.

Statistical analysis

The associations between breastfeeding exposure variables and asthma were modeled using logistic regression; allergic and nonallergic asthma phenotypes were modeled using multinomial logistic regression, with children without asthma as the reference group. The regression models included only participants with complete data on exposure, outcomes, and confounding variables. Potential confounding variables were identified on the basis of existing literature and constructing a directed acyclic graph (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).²⁸ Covariates were included in the final adjusted model using the disjunctive cause criterion approach if they were a common cause of the exposure, or the outcome, or both.²⁹ Each model was adjusted for child's sex, mode of delivery, gestational age at delivery, low birth weight, maternal age at birth, maternal smoking during pregnancy, parental ethnicity, family socioeconomic status (socio-economic indexes for areas—a summary measure of socioeconomic conditions),³⁰ maternal asthma, paternal asthma, family history of allergic disease, number of siblings, childcare attendance, and exposure to environmental smoking in first year of life. The model of duration of overall breastfeeding was additionally adjusted for age of introduction to solids.

We hypothesized that a diagnosis of eczema during breastfeeding may impact a mother's behavior surrounding duration of breastfeeding. Models for the association between breastfeeding practices and asthma outcomes were therefore stratified by whether the infant received a diagnosis of eczema during the breastfeeding period, that is, no eczema diagnosis, eczema diagnosed during breastfeeding, and eczema diagnosis after cessation of breastfeeding. The rationale behind this stratification is that a diagnosis of eczema after cessation of breastfeeding would not have influenced breastfeeding practices. In addition, we conducted a sensitivity analysis excluding participants who were reported to have wheezed in the first year of life to assess for the possibility of further reverse causality in which mothers prolonged breastfeeding in infants with early signs of wheeze. Unfortunately, because of the absence of data on age of wheezing in infancy, early wheeze could not be examined in the same manner as eczema. Finally, to assess for possible attrition bias in the follow-up of the HealthNuts participants, characteristics of those who did and did not participate in the

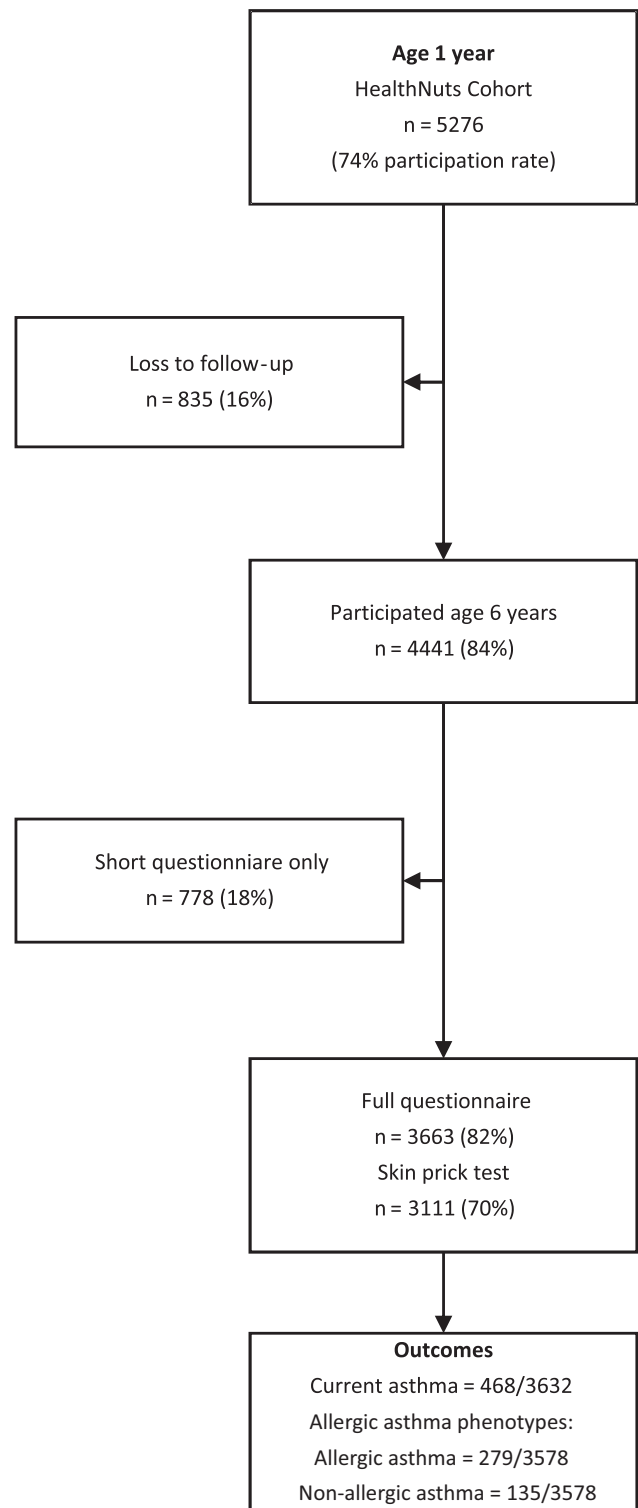


FIGURE 1. Study population and follow-up at age 6 years.

full questionnaire were compared using Pearson χ^2 test for categorical variables and Student t test for continuous variables. Inverse probability weights were generated for factors that were associated with participation, and were applied to all logistic regression models.³¹ Stata software (version 15.1, StataCorp, College Station, Texas) was used for all analysis.

TABLE I. Breastfeeding and diagnosis of eczema during the breastfeeding period, among children with and without current asthma

Characteristic	Total* (N = 3632)	No asthma (n = 3164)	Asthma (n = 468)	P value
Breastfeeding ever				
No	141	83% (117)	17% (24)	.1
Yes	3428	87% (2993)	13% (435)	
Overall breastfeeding duration (mo)				
<3	661	87% (527)	13% (89)	.4
3-<6	441	85% (375)	15% (66)	
6-<12	1040	88% (915)	12% (125)	
≥12	1344	88% (1176)	12% (168)	
Overall breastfeeding duration (mo), mean ± SD	10.0 ± 5.9	10.0 ± 5.9	9.7 ± 6.0	.3
Exclusive breastfeeding duration (mo)				
Never	819	86% (708)	14% (111)	.3
1-≤3	468	85% (399)	15% (69)	
4-≤5	1060	88% (936)	12% (124)	
≥6	743	88% (654)	12% (89)	
Overall exclusive breastfeeding duration (mo), mean ± SD	3.3 ± 2.4	3.4 ± 2.4	3.2 ± 2.4	.2
Parent-reported eczema diagnosis				
No eczema	2362	90% (2120)	10% (242)	<.001
Eczema diagnosed before breastfeeding cessation	700	81% (566)	19% (134)	
Eczema diagnosed after breastfeeding cessation	243	82% (199)	18% (44)	

*The total for each variable may not add up to the total of 3632 because of missing data.

Ethics

Approval to conduct the HealthNuts Study was obtained from the Victorian State Government Office for Children (reference no. CDF/07/492), the Victorian State Government Department of Human Services (reference no. 10/07), and the Royal Children's Hospital Human Research Ethics Committee (reference no. 27047 and 32294).

RESULTS

Study population and participation

Of the original 5276 HealthNuts participants recruited at age 1 year, 4441 (84%) participated at age 6 years, with 3663 (82%) completing the full questionnaire and 3111 (70%) undergoing SPT (Figure 1). Children who did not participate in the full questionnaire at age 6 years were more likely to be never breast-fed, from a lower socioeconomic background, have 1 or both parents born outside of Australia, have no family history of allergic disease, and exposed to prenatal maternal or environmental smoking, than those who participated with full data (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Among children with asthma data (n = 3632), breastfeeding was initiated in 96%. The mean length of exclusive feeding was 3.4 ± 2.4 months and 10.0 ± 5.9 months for overall duration (Table I). At age 6 years, the prevalence of current asthma was 13% (95% CI, 12%-14%). Of the 468 children with current asthma, 414 (88%) also had data on sensitization; based on this, the prevalence of allergic and nonallergic asthma was 8% (95% CI, 7%-9%; n = 279 of 3578) and 4% (95% CI, 3%-5%; n = 135 of 3578), respectively. Children with asthma were more likely to be male, have a maternal or paternal history of asthma, a family history of allergic disease, born preterm (≤36 weeks gestation), born via cesarean section, and exposed to maternal smoking during pregnancy (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

Breastfeeding, asthma and asthma phenotypes

Of those ever breast-fed, 13% of children had current asthma at age 6 years compared with 16% of those never breast-fed. There was little evidence of an association between breastfeeding ever, duration of overall breastfeeding or duration of exclusive breastfeeding, and the outcome of asthma, although the adjusted odds ratio (aOR) suggests a possible inverse association but was imprecise (Table II). When asthma was further stratified into allergic and nonallergic phenotypes, there was still little evidence of an association between ever breastfeeding, overall duration, or increased length of exclusive breastfeeding for allergic and nonallergic asthma phenotypes (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

Stratification by eczema diagnosis during breastfeeding

A total of 3632 children had information on their asthma status and of these 3305 also had information on their eczema status including age of diagnosis; 71.5% had no eczema in the first year of life (n = 2362 of 3305), 21.2% received a diagnosis of eczema during breastfeeding (n = 700 of 3305), and 7.3% were diagnosed with eczema after the cessation of breastfeeding (n = 243 of 3305); these children were breast-fed for an average of 9.9 ± 5.9 months, 12.5 ± 4.7 months, and 3.2 ± 2.8 months, respectively.

Increased duration of breastfeeding was associated with reduced odds of asthma among children without a diagnosis of eczema in the first year of life (per 1-month increase, aOR, 0.98; 95% CI, 0.95-1.0; P = .05). This equates to a 0.86 (95% CI, 0.74-1.0) reduction in odds of asthma for 6-month additional breastfeeding. There was little evidence of an association between increased duration of breastfeeding and asthma among children who were diagnosed with eczema during breastfeeding or after cessation of breastfeeding (aOR, 1.03, 95% CI, 0.98-1.08,

TABLE II. Association between breastfeeding and current asthma at age 6 y

Breastfeeding definitions	N*	% asthma	Crude OR (95% CI)	P value	aOR† (95% CI)	P value
Breastfeeding ever						
No	123	16%	1.0		1.0	
Yes	3065	13%	0.76 (0.47-1.24)	.3	0.76 (0.45-1.29)	.3
Overall breastfeeding duration (mo)						
<3	588	14%	1.0		1.0	
3-≤6	377	14%	0.98 (0.67-1.43)	.9	0.94 (0.64-1.40)	.8
6-≤12	887	12%	0.86 (0.63-1.17)	.3	0.89 (0.64-1.23)	.5
≥12	1161	12%	0.89 (0.67-1.20)	.4	0.91 (0.67-1.24)	.5
Per 1-mo increase			0.99 (0.98-1.01)	.5	0.99 (0.98-1.01)	.6
Exclusive breastfeeding duration (mo)						
Never	737	14%				
1-≤3	424	15%	1.12 (0.80-1.57)	0.5	1.19 (0.84-1.71)	.3
4-≤5	968	11%	0.82 (0.61-1.09)	.2	0.87 (0.64-1.18)	.4
≥6	667	12%	0.88 (0.65-1.21)	.4	0.93 (0.66-1.29)	.7
Per 1-mo increase			0.97 (0.93-1.02)	.2	0.98 (0.93-1.03)	.4

OR, Odds ratio.

*The sample size reported includes only those with complete data on exposure, outcome, and covariates adjusted for.

†All analyses adjusted for sex, mode of delivery, age of gestation, low birth weight, maternal age at gestation, maternal smoking during pregnancy, parental country of birth, family socioeconomic status, maternal asthma, paternal asthma, family history of atopy, number of siblings, environmental smoking in first year of life, and childcare attendance in first year of life. Overall breastfeeding duration was additionally adjusted for age of solids introduction. All adjusted models have been reweighted for factors associated with participation in wave 3 of study using inverse probability weights.

$P = .3$, and aOR, 0.96, 95% CI, 0.81-1.13, $P = .6$, respectively) (Table III; Figure 2). There was weak evidence that increased duration of breastfeeding may be associated with reduced odds of allergic asthma among children without eczema (aOR, 0.97; 95% CI, 0.94-1.01; $P = .1$); this association was not evident for the other eczema strata (Table III). There was little evidence of an association between duration of breastfeeding and nonallergic asthma and duration of exclusive breastfeeding and asthma or the asthma phenotypes, among each of the eczema strata. However, comparisons were hindered by reduced sample size, particularly in the nonallergic asthma phenotype and eczema diagnosed after breastfeeding cessation strata.

Sensitivity analyses

A sensitivity analysis was conducted that excluded infants with wheeze in the first year of life ($n = 544$ for participants with data on asthma outcomes as well as duration of breastfeeding data at age 6 years). Some variation in estimates of the magnitude of associations compared with the primary analysis was observed, likely due to the change in sample size; however CIs remained wide and included the null value (data not shown) and conclusions were unchanged. Increased duration of breastfeeding was associated with a reduced risk of asthma in children without eczema, albeit with weaker evidence (aOR, 0.98; 95% CI, 0.95-1.0; $P = .08$). A sensitivity analysis was also conducted combining the no eczema and eczema diagnosed after breastfeeding cessation strata, because the diagnosis of eczema should not have influenced breastfeeding duration (see Table E4 in this article's Online Repository at www.jaci-inpractice.org). The results were largely the same as the no eczema only strata, although precision increased for some estimates likely because of the increased sample size.

DISCUSSION

In this longitudinal, population-based study, a modest protective association was observed between increased duration of overall breastfeeding and asthma, but only among children who were not diagnosed with eczema in the first year of life. Six months of breastfeeding in children without eczema was associated with a 14% reduced odds of asthma, which represents a significant public health gain given the population prevalence of asthma and other known benefits of breastfeeding. There was little evidence of an association between breastfeeding practices and current asthma or allergic asthma phenotypes at age 6 years when not stratified by eczema status or among those who were diagnosed with eczema during breastfeeding or after breastfeeding ceased.

Early signs of allergic diseases, such as eczema, have been shown to increase the likelihood of a mother breastfeeding for longer,²¹ possibly in the hope that it will prevent the development of other allergic diseases or reduce the severity of eczema. Failure to adequately account for this may lead to an attenuation of observable protective associations between breastfeeding and asthma or spurious associations suggesting an increased risk of asthma in those who are breast-fed for longer because of the presence of eczema. In addition, eczema is a known risk factor for asthma and part of the same allergic disease diathesis. Associations observed in children without eczema are unlikely to be influenced by these factors. This analysis was stratified on 3 levels of eczema, that is, no eczema, eczema diagnosed during breastfeeding, and eczema diagnosed after the cessation of breastfeeding. A test for interaction would be inappropriate here because the putative interacting factor, eczema, is not independent of the exposure (breastfeeding duration) and also may be a consequence of a condition (internal allergic state) that is integral to the disease process for the outcome under study (asthma).³²

TABLE III. Association between breastfeeding and asthma or asthma phenotypes, stratified by a diagnosis of eczema during breastfeeding

		No eczema			Eczema diagnosed during breastfeeding				Eczema diagnosed after breastfeeding ceased			
Current asthma	N*	% asthma	aOR (95% CI)	P	N*	% asthma	aOR (95% CI)	P	N*	% asthma	aOR (95% CI)	P
Overall breastfeeding duration (mo)												
<3	412	12%	1.0		16	13%	1.0		136	21%	1.0	
3-<6	255	11%	0.94 (0.57-1.57)	.8	55	22%	1.41 (0.24-8.26)	.7	50	14%	0.68 (0.24-1.90)	.5
6-<12	604	10%	0.88 (0.59-1.33)	.5	208	19%	1.40 (0.25-7.87)	.7	31	16%	0.74 (0.19-2.85)	.7
≥12	780	9%	0.72 (0.48-1.08)	.1	314	20%	1.59 (0.28-8.98)	.6	0	—	NR	
Per 1-mo increase			0.98 (0.95-1.00)	.05			1.03 (0.98-1.08)	.3			0.96 (0.81-1.13)	.6
Exclusive breastfeeding duration (mo)												
Never	476	11%	1.0		90	22%	1.0		120	18%	1.0	
1-≤3	294	12%	1.14 (0.72-1.81)	.6	69	25%	1.10 (0.46-2.62)	.8	39	21%	1.38 (0.51-3.72)	.5
4-≤5	661	10%	0.85 (0.58-1.27)	.4	214	16%	0.78 (0.38-1.59)	.5	36	14%	0.75 (0.21-2.64)	.6
≥6	455	10%	0.87 (0.56-1.34)	.5	173	19%	0.81 (0.39-1.69)	.6	12	25%	1.36 (0.28-6.55)	.7
Per 1-mo increase			0.97 (0.91-1.03)	.3			0.96 (0.86-1.07)	.5			1.00 (0.82-1.22)	1.0

		No eczema			Eczema diagnosed during breastfeeding				Eczema diagnosed after breastfeeding ceased			
Allergic asthma	N*	% asthma	aOR† (95% CI)	P	N*	% asthma	aOR† (95% CI)	P	N*	% asthma	aOR† (95% CI)	P
Overall breastfeeding duration (mo)												
<3	405	5%	1.0		16	13%	1.0		134	16%	1.0	
3-<6	253	5%	1.04 (0.49-2.19)	.9	55	20%	1.01 (0.16-6.36)	.9	49	6%	0.26 (0.06-1.16)	.1
6-<12	598	6%	1.18 (0.67-2.08)	.6	205	15%	0.85 (0.14-5.00)	.9	30	10%	0.57 (0.13-2.39)	.4
≥12	771	4%	0.74 (0.41-1.36)	.2	305	15%	0.91 (0.15-5.42)	.9	0	—	NR	
Per 1-mo increase			0.97 (0.94-1.01)	.1			1.01 (0.96-1.06)	.8			0.87 (0.70-1.07)	.2
Exclusive breastfeeding duration (mo)												
Never	467	5%	1.0		88	18%	1.0		119	14%	1.0	
1-≤3	291	5%	1.05 (0.54-2.06)	.9	66	20%	1.02 (0.38-2.74)	1.0	37	11%	0.97 (0.27-3.52)	1.0
4-≤5	658	5%	0.9 (0.53-1.53)	.7	212	14%	0.72 (0.32-1.59)	.4	35	9%	0.59 (0.14-2.49)	.5
≥6	447	5%	0.73 (0.37-1.41)	.3	170	15%	1.14 (0.5-2.61)	.7	12	17%	1.49 (0.26-8.49)	.7
Per 1-mo increase			0.96 (0.88-1.05)	.4			1.0 (0.88-1.14)	1.0			0.94 (0.74-1.20)	.6

		No eczema			Eczema diagnosed during breastfeeding				Eczema diagnosed after breastfeeding ceased			
Nonallergic asthma	N*	% asthma	aOR† (95% CI)	P	N*	% asthma	aOR† (95% CI)	P	N*	% asthma	aOR† (95% CI)	P
Overall breastfeeding duration (mo)												
<3	405	5%	1.0		16	0%	1.0		134	3%	1.0	
3-<6	253	6%	1.00 (0.49-2.01)	1.0	55	2%	Omitted	—	49	6%	3.08 (0.18-53.62)	.4
6-<12	598	3%	0.72 (0.38-1.37)	.4	205	2%	Omitted	—	30	3%	0.27 (0.00-28.17)	.6
≥12	771	4%	0.73 (0.41-1.33)	.4	306	3%	Omitted	—	—	—	—	
Per 1-mo increase			0.98 (0.94-1.02)	.3			1.11 (0.97-1.27)	.1			1.15 (0.72-1.82)	.6
Exclusive breastfeeding duration (mo)												
Never	467	4%	1.0		88	5%	1.0		119	3%	1.0	

1-≤3	291	6%	1.36 (0.7-2.62)	.4	66	2%	0.31 (60.02-4.33)	.4	37	5%	1.25 (0.11-13.99)	.86
4-≤5	658	4%	1.08 (0.59-1.97)	.8	212	2%	0.46 (60.08-2.74)	.4	35	3%	1.06 (0.01-119.95)	1.0
≥6	447	3%	0.79 (0.38-1.63)	.5	170	2%	0.41 (0.07-2.28)	.3	12	8%	0.61 (0-171.16)	.9
Per 1-mo increase			0.97 (0.89-1.07)	.6			0.90 (0.68-1.18)	.4			1.05 (0.47-2.35)	.9

NR, Not reported.

*The sample size reported includes only those with complete data on exposure, outcome, and covariates adjusted for.

†All analyses adjusted for sex, mode of delivery, age of gestation, low birth weight, maternal age at gestation, maternal smoking during pregnancy, parental ethnicity, family socioeconomic status, maternal asthma, paternal asthma, family history of atopy, number of siblings, environmental smoking in first year of life, age of solids introduction, and childcare attendance in first year of life. All adjusted models have been reweighted for factors associated with participation in the study using inverse probability weights.

Although there was little evidence of an association between breastfeeding duration and asthma overall, we found evidence that this differed depending on whether the infant had been diagnosed with eczema during breastfeeding. A protective association between increased breastfeeding duration and asthma was observed among children without eczema in the first year of life. In contrast, the direction of association for infants who were diagnosed with eczema during breastfeeding suggested a possible increased risk, although CIs were wide and included the null. This early manifestation of allergic disease may have led mothers to breast-feed for longer, and suggests that without adequately accounting for the presence of early eczema during breastfeeding, estimates may be biased because of reverse causality or potential mediating/confounding effects of eczema.

Infantile eczema is an established risk factor for asthma, and although longer breastfeeding duration may have a protective association in children without eczema, it is difficult to disentangle reverse causality from whether the potential benefit afforded by increased breastfeeding is not sufficient to reduce the risk of asthma in high-risk infants with eczema. There was a small subgroup in this cohort whose members were diagnosed with eczema after the cessation of breastfeeding. These children would be at increased risk of asthma due to the presence of eczema. Because the diagnosis of eczema occurred after the cessation of breastfeeding, breastfeeding practices and their associations are less likely to have been influenced by the eczema diagnosis, although duration of breastfeeding may be acting as a proxy for age at onset of eczema, with earlier onset being associated with a greater risk of asthma. In this subgroup, the direction of effect suggested a protective association between breastfeeding and asthma, but the estimates were too imprecise to infer any conclusions.

A number of studies have observed no association between breastfeeding and asthma, with either increasing overall duration^{10,11,13-16,33} or length of exclusivity.^{5,6,10-15} Differences in the age of populations is another explanation that may explain the discrepancy between our results and other studies. A number of studies conducted in populations age 5 years or less have shown a protective effect of prolonged breastfeeding on asthma.^{3,4,33-35} Asthma is inherently hard to diagnose in this age group given the heterogeneous causes of wheeze in early childhood, the most common being viral respiratory tract infections (RTIs).³⁶ Given that breastfeeding likely protects against RTIs,³⁷ a reduction in RTI-induced wheeze due to breastfeeding may mistakenly be misclassified as a reduction in asthma, thereby overestimating a protective association between breastfeeding and asthma. This potentially explains findings from longitudinal studies that showed a significant protective effect of breastfeeding on asthma in early childhood that attenuated as the child aged.^{7,8} Given that The International Consensus on Paediatric Asthma highlights age 5 years as a turning point for the reliability of an asthma diagnosis³⁸ and our study used a relatively specific definition of doctor-diagnosed asthma, our study is less likely to be subject to such misclassification.

Few studies besides the present analysis have distinguished between the effects of breastfeeding on allergic and nonallergic asthma phenotypes.^{6,8,9} In a cohort of 3781 5-year-olds, Nwaru et al⁶ found that increased length of breastfeeding was protective against nonallergic asthma but not allergic asthma. Nagel et al⁹ found similar results in their much larger multicentered cohort of more than 54,000 children aged 8 to 12 years; however,

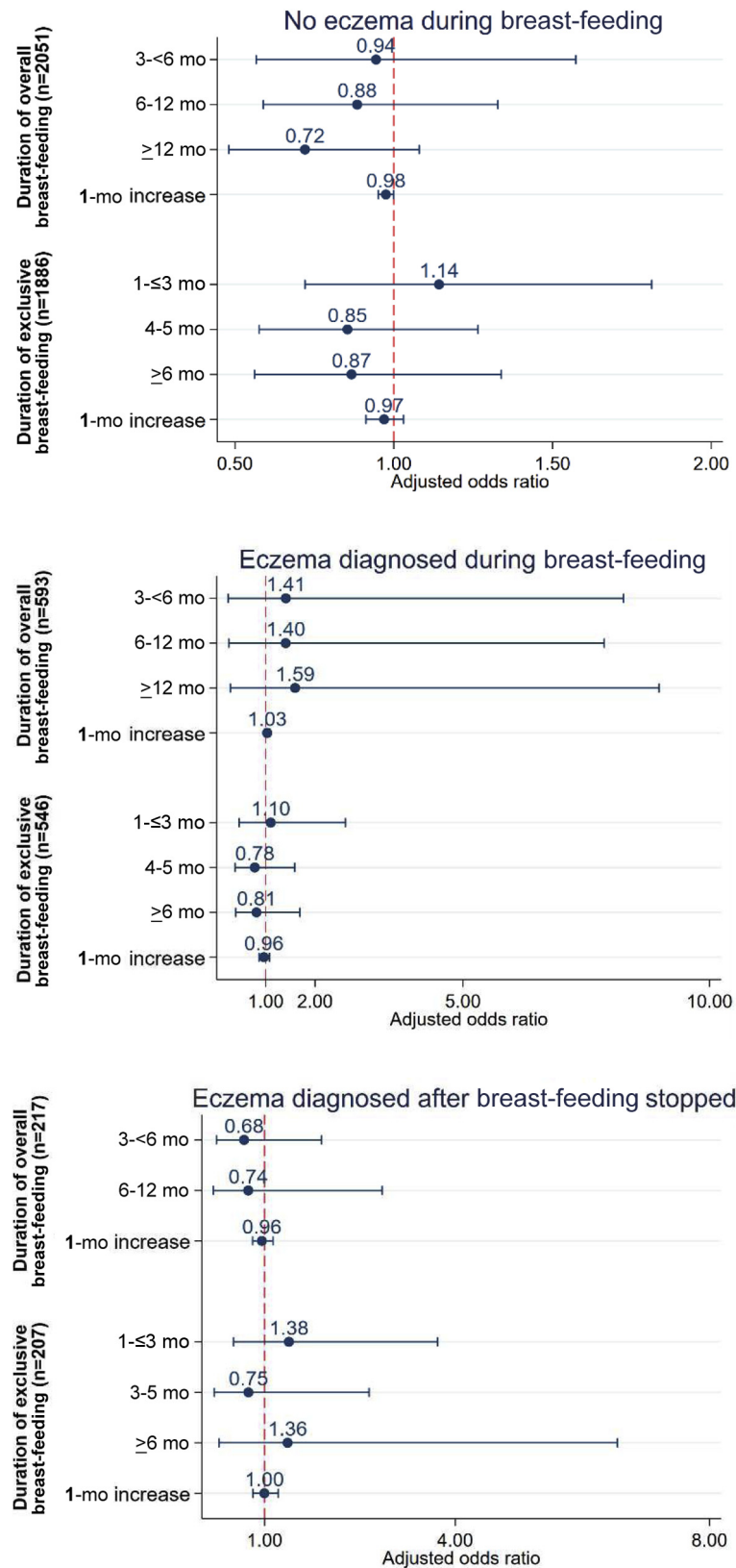


FIGURE 2. Association between breastfeeding and current asthma, stratified by the diagnosis of eczema during breastfeeding.

interestingly, this was significant only in nonaffluent countries. They proposed that protection extended only to nonaffluent countries because they generally have a much higher rate of RTIs.⁹ Given that lung damage has been associated with recurrent RTIs in early childhood,³⁹ the burden of nonatopic asthma is perhaps reduced by this mechanism because breastfeeding reduces the number of RTIs, subsequently reducing the amount of damage to the lungs and improving overall function. This is a possible explanation for the difference in findings in our cohort where no association was observed for nonallergic asthma, who being from an affluent country are less likely to experience the same burden of RTIs. In a Swedish birth cohort, exclusive breastfeeding for at least 4 months was associated with a reduced risk of asthma across the first 8 years, although the association diminished with age, and also a reduced risk of atopic but not nonatopic asthma at age 8 years. These associations were maintained after controlling for disease-related modification of exposure by excluding children with early-life wheeze or eczema.⁸ This inconsistency of results seen across ours and other studies highlights the need for further investigation of the relationship between breastfeeding and asthma phenotypes, using larger populations of asthmatic patients with known phenotypes and accounting for the influence of infantile eczema on breastfeeding practices.

Strengths of this study include the use of a large, prospective cohort with population-based sampling. Because objectively measuring asthma at the population level is challenging due to the absence of a criterion standard test and heterogeneity in the presentation of asthma, we used parent report of doctor diagnosis of asthma in conjunction with current symptoms and/or medication used to describe the prevalence of asthma. Self-reported doctor diagnosis of asthma has high specificity and medium to high sensitivity when compared with clinical methods of diagnosing asthma.^{40,41} Reporting asthma in young children (<5 years) can be problematic because it is difficult to untangle true asthma from early transient wheeze of viral origin; it is a strength of the present study that asthma has been diagnosed by a doctor in children at age 6 years. Finally, we used SPT to differentiate between allergic and nonallergic asthma, allowing individual analysis comparing the effect of breastfeeding on each phenotype.

We acknowledge that limitations exist with these results. Although initial recruitment was high, we used strict inclusion criteria to include only those who completed the long questionnaire and SPT with complete data at age 6 years. Therefore, there remains the possibility of attrition bias given a number of significant differences in the demographic characteristics between this group and those excluded. An approach to dealing with selective attrition is to reweight the sample included in the analysis to reflect the distribution of characteristics of the original cohort, where there was a significant difference between baseline factors of participant and non-participants. We used inverse probability weighting, which aims to give greater weight to participants whose characteristic profile is less represented in the follow-up.⁴² Second, breastfeeding practices and eczema were reported at age 1 year, which may be affected by recall error. The lack of prospective collection of breastfeeding and eczema-onset data in the first year of life does not allow for a more direct assessment of the temporal sequence of these events or exploration of early-life eczema impacting on duration of breastfeeding.

Finally, although we adjusted for a wide range of confounding variables, residual effect by unknown factors remains a possibility.

Disentangling these findings is complex because infantile eczema is a known risk factor for asthma, is part of the same allergic disease diathesis, and has been shown to influence breastfeeding choices. Associations observed in children without eczema are unlikely to be influenced by these factors. We observed that increased duration of overall breastfeeding conferred a modest protective association against the development of asthma in children without eczema in the first year of life; however, this association was masked before stratification by eczema status. Future studies examining breastfeeding practices and the risk of allergic outcomes in childhood need to consider the presence of early-life allergic manifestations and possible disease-related modification of exposure.

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REFERENCES

- Horta BL, Victora CG. Short-term effects of breastfeeding: a systematic review on the benefits of breastfeeding on diarrhoea and pneumonia mortality. Geneva, Switzerland: World Health Organization; 2013.
- Horta BL, Victora CG. Long term effects of breastfeeding: a systematic review. Geneva, Switzerland: World Health Organization; 2013.
- Klopp A, Vehling L, Becker AB, Subbarao P, Mandhane PJ, Turvey SE, et al. Modes of infant feeding and the risk of childhood asthma: a prospective birth cohort study. *J Pediatr* 2017;190:192-199.e2.
- Huang C, Liu W, Cai J, Weschler LB, Wang X, Hu Y, et al. Breastfeeding and timing of first dietary introduction in relation to childhood asthma, allergies, and airway diseases: a cross-sectional study. *J Asthma* 2017;54:488-97.
- den Dekker HT, Sonnenschein-van der Voort AM, Jaddoe VW, Reiss IK, de Jongste JC, Duijts L. Breastfeeding and asthma outcomes at the age of 6 years: The Generation R Study. *Pediatr Allergy Immunol* 2016;27:486-92.
- Nwaru BI, Takkinen HM, Niemela O, Kaila M, Erkkola M, Ahonen S, et al. Timing of infant feeding in relation to childhood asthma and allergic diseases. *J Allergy Clin Immunol* 2013;131:78-86.
- Silvers KM, Frampton CM, Wickens K, Pattermore PK, Ingham T, Fishwick D, et al. Breastfeeding protects against current asthma up to 6 years of age. *J Pediatr* 2012;160:991-996.e1.
- Kull I, Melen E, Alm J, Hallberg J, Svartengren M, van Hage M, et al. Breastfeeding in relation to asthma, lung function, and sensitization in young schoolchildren. *J Allergy Clin Immunol* 2010;125:1013-9.
- Nagel G, Buchele G, Weinmayr G, Bjorksten B, Chen YZ, Wang H, et al. Effect of breastfeeding on asthma, lung function and bronchial hyperreactivity in ISAAC phase II. *Eur Respir J* 2009;33:993-1002.
- Elliott L, Henderson J, Northstone K, Chiu GY, Dunson D, London SJ. Prospective study of breastfeeding 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.e1-e3.

11. Nwaru BI, Craig LC, Allan K, Prabhu N, Turner SW, McNeill G, et al. Breastfeeding and introduction of complementary foods during infancy in relation to the risk of asthma and atopic diseases up to 10 years. *Clin Exp Allergy* 2013;43:1263-73.
12. Kramer MS, Matush L, Bogdanovich N, Aboud F, Mazer B, Fombonne E, et al. Health and development outcomes in 6.5-y-old children breastfed exclusively for 3 or 6 mo. *Am J Clin Nutr* 2009;90:1070-4.
13. Miyake Y, Tanaka K, Sasaki S, Kiyohara C, Ohya Y, Fukushima W, et al. Breastfeeding and the risk of wheeze and asthma in Japanese infants: the Osaka Maternal and Child Health Study. *Pediatr Allergy Immunol* 2008;19:490-6.
14. Vanmeel E, van Meel E, de Jong M, Elbert N, den Dekker H, Reiss I, et al. Duration and exclusiveness of breastfeeding and school-age lung function and asthma. *Ann Allergy Asthma Immunol* 2017;119:21-26.e2.
15. Morales-Romero CJ, Bedolla-Barajas M, Lopez-Vargas L, Romero-Velarde CE. Prevalence of allergic diseases and their association with breastfeeding and initiation of complementary feeding in school-age children of Ciudad Guzman, Mexico. *Arch Argent Pediatr* 2015;113:324-30.
16. Sears MR, Greene JM, Willan AR, Taylor DR, Flannery EM, Cowan JO, et al. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. *Lancet* 2002;360:901-7.
17. Wright AL, Holberg CJ, Taussig LM, Martinez FD. Relationship of infant feeding to recurrent wheezing at age 6 years. *Arch Pediatr Adolesc Med* 1995;149:758-63.
18. Lodge CJ, Tan DJ, Lau MX, Dai X, Tham R, Lowe AJ, et al. Breastfeeding and asthma and allergies: a systematic review and meta-analysis. *Acta Paediatr* 2015;104:38-53.
19. Flohr C, Henderson AJ, Kramer MS, Patel R, Thompson J, Rifas-Shiman SL, et al. Effect of an intervention to promote breastfeeding on asthma, lung function, and atopic eczema at age 16 years: follow-up of the PROBIT randomized trial. *JAMA Pediatr* 2018;172:e174064.
20. Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ. Atopic dermatitis and the atopic march revisited. *Allergy* 2014;69:17-27.
21. Lowe AJ, Carlin JB, Bennett CM, Abramson MJ, Hosking CS, Hill DJ, et al. Atopic disease and breastfeeding—cause or consequence? *J Allergy Clin Immunol* 2006;117:682-7.
22. Ronmark E, Jonsson E, Platts-Mills T, Lundback B. Different pattern of risk factors for atopic and nonatopic asthma among children—report from the Obstructive Lung Disease in Northern Sweden Study. *Allergy* 1999;54:926-35.
23. García Marcos L, Castro Rodríguez J, Suarez Varela M, Garrido J, Hernandez G, Gimeno A, et al. A different pattern of risk factors for atopic and non-atopic wheezing in 9-12-year-old children. *Pediatr Allergy Immunol* 2005;16:471-7.
24. Koplin JJ, Wake M, Dharmage SC, Matheson M, Tang ML, Gurrin LC, et al. Cohort profile: the HealthNuts study: population prevalence and environmental/genetic predictors of food allergy. *Int J Epidemiol* 2015;44:1161-71.
25. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol* 2011;127:668-676.e1-676.e2.
26. Suaini NHA, Koplin JJ, Peters RL, Sasaki M, Ellis JA, Martino DJ, et al. Children with East Asian-born parents have an increased risk of allergy but may not have more asthma in early childhood. *J Allergy Clin Immunol Pract* 2019;7:539-547.e3.
27. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;8:483-91.
28. Textor J, van der Zander B, Gilthorpe MS, Liskiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. *Int J Epidemiol* 2016;45:1887-94.
29. VanderWeele TJ. Principles of confounder selection. *Eur J Epidemiol* 2019;34:211-9.
30. The Index of Relative Socio-economic Disadvantage. Australian Bureau of Statistics. Available at: www.abs.gov.au/ausstats/abs@.nsf/Lookup/2033.0.55.001main1features100052011. Accessed June 6, 2013.
31. Williamson EJ, Forbes A. Introduction to propensity scores. *Respirology* 2014;19:625-35.
32. Dudbridge F, Fletcher O. Gene-environment dependence creates spurious gene-environment interaction. *Am J Hum Genet* 2014;95:301-7.
33. Tanaka K, Miyake Y, Sasaki S. Association between breastfeeding and allergic disorders in Japanese children. *Int J Tuberculosis Lung Dis* 2010;14:513-8.
34. Qu F, Weschler LB, Sundell J, Zhang Y. Increasing prevalence of asthma and allergy in Beijing pre-school children: is exclusive breastfeeding for more than 6 months protective? *Chinese Sci Bull* 2013;58:4190-202.
35. Ehlayel M, Bener A. Duration of breastfeeding and the risk of childhood allergic diseases in a developing country. *Allergy Asthma Proc* 2008;29:386-91.
36. Skytt N, Bonnelykke K, Bisgaard H. "To wheeze or not to wheeze": that is not the question. *J Allergy Clin Immunol* 2012;130:403-407.e5.
37. Tromp I, Kiefte-de Jong J, Raat H, Jaddoe V, Franco O, Hofman A, et al. Breastfeeding and the risk of respiratory tract infections after infancy: the Generation R study. *PLoS One* 2017;12:e0172763.
38. Papadopoulos NG, Arakawa H, Carlsen KH, Custovic A, Gern J, Lemanske R, et al. International consensus on (ICON) pediatric asthma. *Allergy* 2012;67:976-97.
39. Gern JE, Rosenthal LA, Sorkness RL, Lemanske RF Jr. Effects of viral respiratory infections on lung development and childhood asthma. *J Allergy Clin Immunol* 2005;115:668-74.
40. Lundback B, Backman H, Lotvall J, Ronmark E. Is asthma prevalence still increasing? *Expert Rev Respir Med* 2016;10:39-51.
41. Jenkins MA, Clarke JR, Carlin JB, Robertson CF, Hopper JL, Dalton MF, et al. Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol* 1996;25:609-16.
42. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. *Stat Methods Med Res* 2011;22:278-95.

ONLINE REPOSITORY

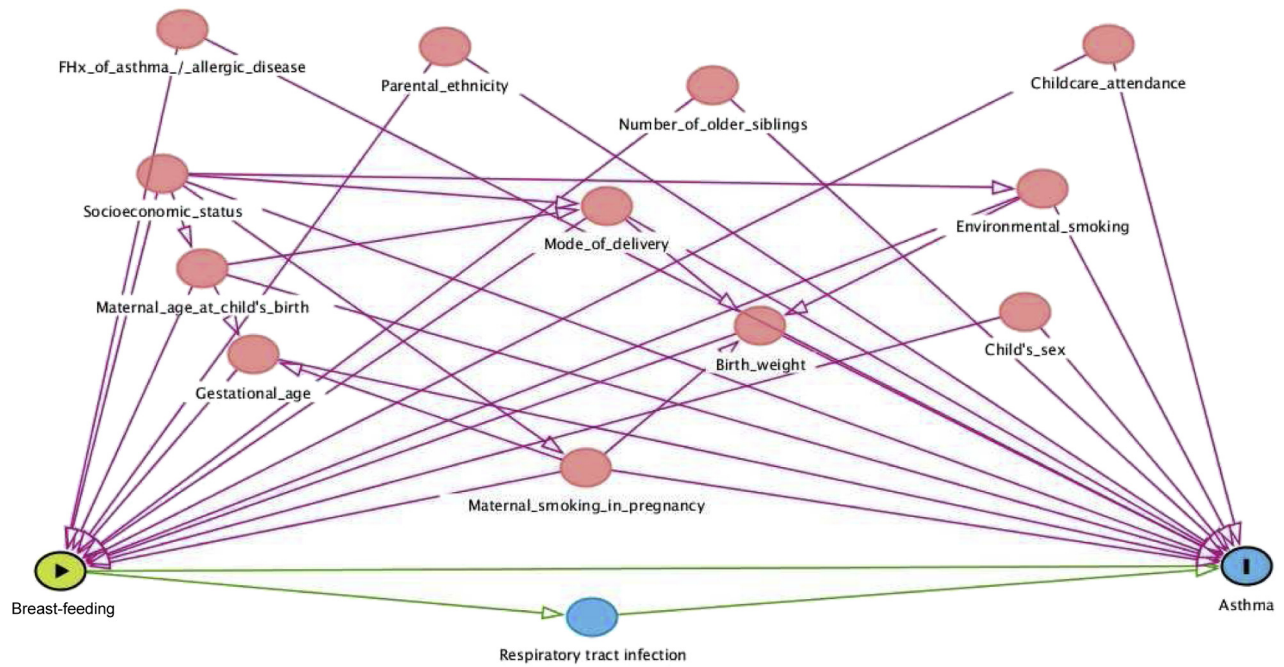


FIGURE E1. Directed acyclic graph generated to inform confounder selection. FHx, family history of allergy.

TABLE E1. Comparison of demographic characteristics between those who did and did not participate at age 6 y

Characteristic	Did not participate in full questionnaire at age 6 y (n = 1613)	Participated in full questionnaire at age 6 y (n = 3663)	P value
Sex (male)	49% (784 of 1601)	52% (1881 of 3643)	.076
Mode of delivery (cesarean)	34% (543 of 1594)	33% (1199 of 3650)	.390
Preterm birth (≤ 36 wk)	6% (93 of 1511)	6% (212 of 3495)	.904
Birth weight (< 2500 g)	6% (93 of 1572)	5% (170 of 3594)	.074
Socioeconomic status (SEIFA)			
1 (most disadvantaged)	25% (398 of 1604)	18% (664 of 3657)	$< .001$
2	19% (309 of 1604)	20% (741 of 3657)	
3	19% (310 of 1604)	22% (792 of 3657)	
4	18% (283 of 1604)	20% (736 of 3657)	
5 (least disadvantaged)	19% (304 of 1604)	20% (724 of 3657)	
Parent country of birth			
Both Australian	53% (814 of 1542)	62% (2209 of 3556)	$< .001$
One or both Asian	12% (183 of 1542)	10% (352 of 3556)	
Other	35% (545 of 1542)	28% (1540 of 3556)	
Maternal age at birth (mo), mean $\pm$ SD	32.2 $\pm$ 5.3	33.3 $\pm$ 4.5	$< .001$
Family history of allergic disease			
Maternal asthma	13% (203 of 1613)	16% (584 of 3663)	.002
Paternal asthma	11% (179 of 1613)	15% (535 of 3663)	.001
Family history of any allergy	63% (1017 of 1613)	72% (2644 of 3663)	$< .001$
Ever breast-fed	91% (1406 of 1551)	96% (3456 of 3599)	$< .001$
Overall breastfeeding duration (mo)			
< 3	24% (360 of 1502)	16% (550 of 3516)	$< .001$
3- < 6	16% (238 of 1502)	13% (452 of 3516)	
6- < 12	27% (404 of 1502)	28% (981 of 3516)	
≥ 12	33% (500 of 1502)	44% (1533 of 3516)	
Overall breastfeeding duration (mo), mean $\pm$ SD	8.5 $\pm$ 6.2	10.0 $\pm$ 5.9	$< .001$
Exclusive breastfeeding duration (mo)			
Never	35% (459 of 1329)	27% (829 of 3117)	$< .001$
< 6	45% (599 of 1329)	49% (1540 of 3117)	
≥ 6	20% (271 of 1329)	24% (748 of 3117)	
Any siblings	52% (838 of 1604)	50% (1809 of 3647)	.078
Maternal smoking in pregnancy	7% (113 of 1548)	4% (126 of 3569)	$< .001$
Environmental smoking at age 1 y	28% (451 of 1590)	19% (676 of 3644)	$< .001$
Wheeze in first year	19% (261 of 1379)	17% (560 of 3224)	.206
Bronchiolitis in first year	14% (207 of 1470)	14% (484 of 3343)	.718

SEIFA, socio-economic indexes for areas.

Factors included in the inverse probability weighting model: sex, low birth weight, SEIFA, parent's country of birth, maternal and paternal history of asthma, family history of any allergy, breastfeeding duration, any siblings, exposure to environmental smoking in first year, and maternal smoking during pregnancy.

TABLE E2. Population demographic characteristics by current diagnosed asthma status

Characteristic	Total (N = 3632)	No asthma (n = 3164)	Asthma (n = 468)	P value
Sex				
Male	1865	84%	16%	<.001
Female	1747	90%	10%	
Maternal history of asthma				
No	3053	89%	11%	<.001
Yes	579	78%	22%	
Paternal history of asthma				
No	3102	88%	12%	<.001
Yes	530	80%	20%	
Family history of allergic disease				
No	1005	89%	11%	.009
Yes	2627	86%	14%	
Preterm birth (≤ 36 wk)				
No	3255	87%	13%	.035
Yes	210	82%	18%	
Mode of infant delivery				
Vaginal	2427	88%	12%	.012
Cesarean section	1192	85%	15%	
Infant birth weight (g)				
<2500	169	83%	17%	.2
≥ 2500	3564	87%	13%	
Maternal age at birth (y), mean $\pm$ SD	33.3 $\pm$ 4.5	33.3 $\pm$ 4.5	33.5 $\pm$ 4.4	.3
No. of siblings				
0	1810	88%	12%	.8
1	1188	87%	13%	
2	452	87%	13%	
3 or more	22	85%	15%	
Parental country of birth				
Both Australian	2192	87%	13%	.7
One/both east Asian	348	89%	11%	
Other	987	87%	13%	
Socioeconomic status via SEIFA quintiles				
1 (least disadvantaged)	656	86%	14%	.5
2	735	86%	14%	
3	787	87%	13%	
4	729	89%	11%	
5 (most disadvantaged)	719	87%	13%	
Maternal smoking during pregnancy				
No	3414	88%	12%	<.001
Yes	125	77%	23%	
Tobacco smoke exposure in first year of life				
No	2943	87%	13%	.4
Yes	670	86%	14%	
Wheeze in first year of life				
No	2644	89%	11%	<.001
Yes	555	78%	22%	
Bronchiolitis in first year of life				
No	2834	89%	11%	<.001
Yes	482	79%	21%	
Childcare attendance in first year of life				
No	2593	87%	13%	.6
Yes	959	88%	12%	
Pet cat in first year of life				
No	3009	87%	13%	.4
Yes	622	88%	12%	

(continued)

TABLE E2. (Continued)

Characteristic	Total (N = 3632)	No asthma (n = 3164)	Asthma (n = 468)	P value
Pet dog in first year of life				
No	2486	87%	13%	.1
Yes	1145	88%	12%	

SEIFA, socio-economic indexes for areas.

TABLE E3. Association between breastfeeding and allergic and nonallergic asthma phenotypes at age 6 y, with children without asthma as the reference group

		Allergic asthma					Nonallergic asthma				
	N	%	Crude OR (95% CI)	P value	aOR* (95% CI)	P value	%	Crude OR (95% CI)	P value	aOR* (95% CI)	P value
Breastfeeding definitions											
Breastfeeding ever											
No	121	10%	1.0		1.0		5%	1.0		1.0	
Yes	3022	8%	0.76 (0.41-1.40)	.4	0.69 (0.36-1.32)	.3	4%	0.74 (0.32-1.72)	.5	0.83 (0.33-2.09)	.7
Overall duration (mo)											
<3	579	8%	1.0		1.0		5%	1.0		1.0	
3-<6	373	8%	1.00 (0.62-1.63)	.99	0.87 (0.53-1.43)	.6	5%	1.04 (0.56-1.91)	.9	1.08 (0.57-2.03)	.8
6-<12	877	8%	1.01 (0.68-1.49)	.99	0.96 (0.65-1.43)	.8	3%	0.65 (0.38-1.12)	.1	0.77 (0.43-1.36)	.4
≥12	1143	7%	0.94 (0.65-1.37)	.8	0.89 (0.60-1.32)	.6	4%	0.78 (0.47-1.27)	.3	0.89 (0.52-1.52)	.7
Per 1-mo increase			1.0 (0.97-1.02)	.8	0.99 (0.97-1.21)	.6		0.99 (0.96-1.02)	.5	1.00 (0.96-1.03)	.8
Exclusive breastfeeding duration (mo)											
Never	727	9%	1.0		1.0		4%	1.0		1.0	
1-≤3	415	8%	0.95 (0.62-1.48)	.8	1.05 (0.67- 1.66)	.8	5%	1.33 (0.74-2.37)	.8	1.37 (0.76-2.47)	.3
4-≤5	961	7%	0.81 (0.57-1.16)	.3	0.85 (0.58-1.25)	.4	4%	0.93 (0.56-1.54)	.4	1 (0.58-1.73)	.99
≥6	656	8%	0.88 (0.6-1.29)	.5	0.92 (0.61-1.38)	.7	3%	0.78 (0.43-1.39)	.7	0.82 (0.44-1.51)	.5
Per 1-mo increase			0.98 (0.92-1.04)	.5	0.98 (0.92-1.04)	.6		0.96 (0.89-1.04)	.9	0.97 (0.90-1.06)	.5

OR, Odds ratio.

*All analyses adjusted for sex, mode of delivery, age of gestation, low birth weight, maternal age at gestation, maternal smoking during pregnancy, parental ethnicity, family socioeconomic status, maternal asthma, paternal asthma, family history of atopy, number of siblings, environmental smoking in first year of life, age of solids introduction, and childcare attendance in first year of life. All adjusted models have been reweighted for factors associated with participation in the study using inverse probability weights.

TABLE E4. Association between breastfeeding and asthma or asthma phenotypes, stratified by no eczema during the breastfeeding period and a diagnosis of eczema during breastfeeding

Current asthma	No eczema or eczema diagnosed after cessation of breastfeeding				Eczema diagnosed during breastfeeding			
	N	% asthma	aOR (95% CI)	P	N	% asthma	aOR (95% CI)	P
Overall breastfeeding duration (mo)								
<3	548	14%	1.0		16	13%	1.0	
3-<6	305	12%	0.84 (0.54-1.31)	.5	55	22%	1.41 (0.24-8.26)	.7
6-<12	635	11%	0.78 (0.54-1.12)	.2	208	19%	1.40 (0.25-7.87)	.7
≥12	780	9%	0.62 (0.43-0.90)	.01	314	20%	1.59 (0.28-8.98)	.6
Per 1-mo increase			0.97 (0.95-0.99)	.005			1.03 (0.98-1.08)	.3
Exclusive breastfeeding duration (mo)								
Never	594	12%	1.0		90	22%	1.0	
1-≤3	333	13%	1.07 (0.71-1.62)	.7	69	25%	1.10 (0.46-2.62)	.8
4-≤5	697	10%	0.79 (0.55-1.14)	.2	214	16%	0.78 (0.38-1.59)	.5
≥6	467	10%	0.82 (0.55-1.23)	.3	173	19%	0.81 (0.39-1.69)	.6
Per 1-mo increase			0.96 (0.91-1.02)	.2			0.96 (0.86-1.07)	.5

Allergic asthma	No eczema or eczema diagnosed after cessation of breastfeeding				Eczema diagnosed during breastfeeding			
	N	% asthma	aOR* (95% CI)	P	N	% asthma	aOR* (95% CI)	P
Overall breastfeeding duration (mo)								
<3	539	8%	1.0		16	13%	1.0	
3-<6	302	5%	0.64 (0.35-1.20)	.2	55	20%	1.01 (0.16-6.36)	.9
6-<12	628	6%	0.78 (0.49-1.23)	.3	205	15%	0.85 (0.14-5.00)	.9
≥12	771	4%	0.47 (0.29-0.78)	.003	305	15%	0.91 (0.15-5.42)	.9
Per 1-mo increase			0.95 (0.92-0.98)	.002			1.01 (0.96-1.06)	.8
Exclusive breastfeeding duration (mo)								
Never	586	7%	1.0		88	18%	1.0	
1-≤3	328	6%	0.88 (0.49-1.57)	.7	66	20%	1.02 (0.38-2.74)	.96
4-≤5	693	5%	0.71 (0.44-1.15)	.2	212	14%	0.72 (0.32-1.59)	.4
≥6	459	5%	0.63 (0.35-1.11)	.1	170	15%	1.14 (0.5-2.61)	.7
Per 1-mo increase			0.93 (0.86-1.00)	.06			1.0 (0.88-1.14)	.0

Nonallergic asthma	No eczema or eczema diagnosed after cessation of breastfeeding				Eczema diagnosed during breastfeeding			
	N	% asthma	aOR* (95% CI)	P	N	% asthma	aOR* (95% CI)	P
Overall breastfeeding duration (mo)								
<3	539	5%	1.0		16	0%	1.0	
3-<6	302	6%	1.38 (0.74-2.59)	.5	55	2%	Omitted	—
6-<12	628	3%	1.15 (0.64-2.06)	.5	205	2%	Omitted	—
≥12	771	4%	0.88 (0.44-1.76)	.6	306	3%	Omitted	—
Per 1-mo increase			0.99 (0.95-1.02)	.5			1.11 (0.97-1.27)	.1
Exclusive breastfeeding duration (mo)								
Never	586	4%	1.0		88	5%	1.0	
1-≤3	328	5%	1.36 (0.7-2.62)	.4	66	2%	0.31 (0.02-4.33)	.4
4-≤5	693	4%	1.08 (0.59-1.97)	.8	212	2%	0.46 (0.08-2.74)	.4
≥6	459	3%	0.79 (0.38-1.63)	.5	170	2%	0.41 (0.07-2.28)	.3
Per 1-mo increase			0.99 (0.91-1.09)	.9			0.90 (0.68-1.18)	.4

*All analyses adjusted for sex, mode of delivery, age of gestation, low birth weight, maternal age at gestation, maternal smoking during pregnancy, parental ethnicity, family socioeconomic status, maternal asthma, paternal asthma, family history of atopy, number of siblings, environmental smoking in first year of life, age of solids introduction, and childcare attendance in first year of life. All adjusted models have been reweighted for factors associated with participation in the study using inverse probability weights.