



# Maternal asthma, breastfeeding, and respiratory outcomes in the first year of life

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## Abstract

Maternal asthma increases the risk of infant wheeze. Breastfeeding may offer protection but there is limited evidence in this high-risk group. We examined associations between breastfeeding and respiratory outcomes, in infants born to women with asthma. This study was a secondary analysis of two prospective cohorts of pregnant women with asthma, and their infants, conducted between 2007 and 2018. At  $6 \pm 1$  (T1) and  $12 \pm 1$  (T2) months post-partum, mothers reported breastfeeding patterns and infant wheeze (primary outcome), bronchiolitis, and related medication use and healthcare utilization, via a validated questionnaire; a subgroup completed face-to-face interviews.  $\chi^2$  tests and logistic regression models, adjusting for confounders, were utilized. Data were complete for 605 participants at T1 and 486 (80%) at T2. Of 605 participants: 89% initiated breastfeeding and 38% breastfed for more than 6 months. Breastfeeding for more than 6 months vs "never" was associated with a reduced adjusted relative risk of infant wheeze at T1 (0.54, 95% confidence interval, 0.30-0.96). Bronchiolitis risk was reduced at T1 and T2 with more than 6 months of breastfeeding vs "never." Breastfeeding duration of 1 to 3 months, 4 to 6 months, and more than 6 months were associated with a reduced risk of infant healthcare utilization (all  $P < .05$ , vs "never"), but not medication use ( $P > .05$ ). Breastfeeding for more than 6 months was associated with a reduced risk of wheeze, bronchiolitis, and wheeze-related healthcare utilization in infants at risk due to maternal asthma. Notably, breastfeeding for shorter durations was associated with a reduced risk of healthcare utilization compared with none. Larger cohorts are needed to further examine the impact of breastfeeding exposure on respiratory health in infants exposed to maternal asthma.

## KEYWORDS

asthma, atopy, breastmilk, bronchiolitis, healthcare, infant/s, maternal, nutrition, offspring, pediatric, respiratory, wheeze

## 1 | INTRODUCTION

Wheeze is highly prevalent worldwide,<sup>1</sup> with a recent meta-analysis demonstrating 36% of infants (95% confidence interval [CI], 35.12-37)

are affected by wheeze in western countries.<sup>2</sup> Maternal asthma increases the odds of infant wheeze and childhood asthma compared with infants not exposed to maternal asthma (odds ratio [OR] 3.04, 95% CI, 2.59-3.56).<sup>3</sup> Wheeze during infancy has also been associated

with an increased risk of chronic wheeze and asthma in school-aged children, as well as a reduction in respiratory ability and function.<sup>4-6</sup> Available management, including pharmacological intervention, may reduce some adverse respiratory symptoms but does not prevent the development of wheeze. Therefore, research related to modifiable risk factors is a public health priority.<sup>7</sup>

Nutrition is a modifiable risk factor that may play an important role in respiratory health including the development of infant wheeze. A major source of nutrition in infancy is breastmilk, with the World Health Organization (WHO) recommending infants be breastfed exclusively for the first 6 months of life, and up to 2 years and beyond with introduced foods.<sup>8,9</sup> Research suggests that breastfeeding may reduce the risk of wheeze in infancy by promoting optimal lung growth and development,<sup>10,11</sup> supporting the immune system and microbiome maturation,<sup>12-14</sup> and by preventing respiratory tract infections.<sup>14,15</sup> However, evidence regarding the beneficial effect of breastfeeding on respiratory health outcomes in childhood is still unclear and, moreover, the evidence in high-risk infants born to women with asthma is lacking.

Systematic reviews examining breastfeeding patterns and childhood asthma/wheeze in general populations have shown breastfeeding to be potentially beneficial for school-aged children.<sup>16-18</sup> Garcia-Larsen et al<sup>16</sup> found that breastfeeding ever vs "never" protects against recurrent wheeze in children aged 5 to 14 years (OR, 0.88, 95% CI, 0.82-0.94, *n* = 25 studies). Dogaru et al<sup>17</sup> concluded that relatively more breastfeeding vs less breastfeeding is protective against wheeze/asthma symptoms in offspring in the age group where breastfeeding exposure is highest (0-2 years) (OR, 0.63, 95% CI, 0.57-0.69, *n* = 14 studies). The third review by Lodge et al provided evidence that any breastfeeding is protective against asthma development in children aged older than 5 years compared with no breastfeeding (OR, 0.88, 95% CI, 0.82-0.95, *n* = 13 studies); a similar result was also found for a breastfeeding duration of more vs less (OR, 0.90 95% CI, 0.84-0.97, *n* = 29 studies).<sup>18</sup> In a meta-analysis stratified by family history of atopy, Gdalevich et al<sup>19</sup> found that breastfeeding more than 3 months vs less than 3 months was protective against childhood asthma (1-10 years) in those with a positive family history (OR, 0.73, 95% CI, 0.62-0.86, *n* = 7 studies). However, the included studies did not specifically examine the impact of maternal asthma, a stronger risk factor than family history of atopy, or even paternal asthma, for the development of wheeze.<sup>2</sup> Furthermore, the examination of wheeze outcomes in the first year of life, when exposure to breastfeeding would be highest and when the incidence/prevalence of wheeze is highest compared with other pediatric age groups, was not conducted.

The Tasmanian Asthma Study (*n* = 8583) observed a lesser risk of current asthma at age 7 in children exposed to maternal asthma that were exclusively breastfed vs those not exposed to exclusive breastfeeding (OR, 0.75, 95% CI, 0.58-0.97).<sup>20</sup> A recent study by Azad et al<sup>21</sup> reported a reduced risk of wheeze with breastfeeding in infants born to mothers with asthma (adjusted risk ratio [aRR] 0.52, 95% CI, 0.35-0.77); this effect was dose-dependent, with exclusive breastfeeding as well as longer duration of any breastfeeding

associated with greater risk reduction. However, no study has examined the effect of breastfeeding on other measures of wheeze severity, such as bronchiolitis, recurrent wheeze, and medication use or healthcare utilization in infancy. Thus, further studies examining the impact of breastfeeding on respiratory health in the first year of life in a group at high risk due to maternal asthma is required.

We hypothesize that exposure to longer durations of breastfeeding are associated with a reduced risk of wheeze in infants born to women with asthma and less severe wheeze (defined by bronchiolitis, recurrent wheeze, healthcare utilization, and medication use) compared with infants breastfed for shorter durations or not at all. Therefore, the primary aim of this study is to examine the association between breastfeeding duration in the first year of life and the incidence of wheeze, in infants born to women with asthma. The secondary aims of this study are to examine the association between breastfeeding and the severity of wheeze in the first year of life.

## 2 | METHODS

Data presented come from the prospective follow-up of infants born to mothers with asthma, who participated in one of two randomized controlled trials (RCTs) of asthma management during pregnancy. Participants were recruited via the antenatal clinics at the John Hunter Hospital, Newcastle, Australia, as part of the Managing Asthma in Pregnancy (MAP) study (June 2007-December 2010) with the primary outcome being the total number of maternal asthma exacerbations.<sup>22</sup> For the Breathing for Life Trial (BLT) (March 2013-June 2018), participants were recruited from antenatal clinics in Newcastle, Sydney, Brisbane, and Canberra, with the primary outcome of this trial being adverse perinatal outcomes.<sup>23</sup> Both studies compared the use of fractional exhaled nitric oxide (FeNO)-guided asthma management during pregnancy to either symptom-based management (MAP) or usual care (BLT). As previously described,<sup>22,23</sup> women older or equal to 18 years of age with physician-diagnosed asthma and use of inhaled therapy ( $\beta$ -agonists, corticosteroids) or asthma symptoms in the past year were recruited between 12 and 22 weeks gestation and followed until delivery; their infants were followed from birth to 12 months of age, with continued follow-up as part of ongoing cohorts. Each study received ethics approval from the Hunter New England Health Human Research Ethics Committee (MAP: 07/02/21/3.06; BLT: 12/10/17/3.04, NSW HREC reference no: HREC/12/HNE/357). Written informed consent was obtained from all participants before enrollment in the RCTs and before infant follow-up.

All outcomes were collected via a validated parent-report questionnaire.<sup>24</sup> The primary outcome for this study is a parent-reported incidence of wheeze, defined as wheeze ever in the first 6  $\pm$  1 months of life (time point 1 [T1]). Parent-reported wheeze, defined as wheeze ever in the first 12  $\pm$  1 months of life (at T2), formed a secondary outcome. Additional secondary outcomes are parent-reported recurrent wheeze (defined as wheeze occurring > 3 times in the last 6 months), incidence of bronchiolitis, healthcare

utilization for wheeze (attending or calling a general practitioner [GP] in an emergency, emergency department [ED] visit, hospital admission, or referral to a consultant in hospital), and medication use for wheeze (short-acting beta-agonists [SABA], inhaled corticosteroid [ICS], or oral corticosteroid [OCS]) at T1 and T2.

The parent-reported questionnaire<sup>24</sup> captured information on breastfeeding initiation ("ever" vs "never") and breastfeeding duration (< 1 month, 1-3 months, 4-6 months, or > 6 months). Information regarding exclusive breastfeeding (number of weeks) was collected at T1, and current breastfeeding status was ascertained at T2, via a structured face-to-face interview with a trained research officer. Women were asked by the research officer "how long was your child exclusively breastfed for?" with exclusive breastfeeding defined as no other solids or liquids given to the infant except breastmilk. Exclusive breastfeeding was then categorized into less than 1 month, 1 to 3 months, or more than or equal to 4 months based on previous studies.<sup>25</sup> Current breastfeeding status was ascertained by asking "is your child currently breastfed?"

Maternal and infant demographics and birth outcomes were collected via medical records or self-report. Maternal weight and height during pregnancy were collected by trained research officers and body mass index (BMI) calculated. Information collected via medical records included gestational age at birth and mode of delivery. Information collected via questionnaire included a number of siblings, the presence of household pets, infant smoke exposure, and maternal age at completion of full-time education. Postcode was collected at baseline and used for socioeconomic status based on Socioeconomic Index for Areas (SEIFA) scores.<sup>26</sup> Smoke exposure was classified as in utero exposure and secondary exposure in infancy (if mother or any member of the household smokes). Infant ethnicity was also collected by self-report from the question "What ethnic group does your family belong to?"

Outcomes were examined using multinomial logistic regression models for breastfeeding duration (categorical) and the dichotomous outcome of wheeze incidence at T1. All secondary outcomes, inclusive of wheeze at T2, recurrent wheeze, bronchiolitis, medication use, and healthcare utilization at T1 and T2, were also examined through regression models. Adjustments were made for known confounders: maternal age, maternal BMI, infant smoke exposure, socioeconomic status, maternal age at completion of full-time education, and mode of delivery.<sup>27-29</sup> Estimated effects are presented as adjusted relative risk with 95% CIs. In a preliminary analysis, we found no association between breastfeeding rates and RCT group allocation ( $P = .80$ ); thus it was not considered to be a confounder to the proposed analyses. Goodness-of-fit was analyzed by a generalized Hosmer-Lemeshow goodness-of-fit test for regression models. Trend analyses were conducted for breastfeeding duration and secondary outcomes. Group differences in wheeze and bronchiolitis incidence according to breastfeeding duration and exclusivity were examined using  $\chi^2$  tests. A  $P$ -value of less than .05 was considered significant, with adjustments for multiple group comparisons. Analyses were performed using STATA IC version 15 (StataCorp, College Station, TX).

### 3 | RESULTS

Questionnaire data was available for  $N = 624$  mother-infant dyads. Complete data for the primary outcome of wheeze and breastfeeding exposure was available for  $n = 605$  (97%) at T1 (mean age  $6.3 \pm 0.7$  months), of which  $n = 486$  (80%) provided data at T2 (mean age  $12.4 \pm 1.1$  months). Characteristics of the 605 mother-infant dyads are shown in Table 1. Mean maternal BMI at enrollment was  $29.9 \pm 8.2$  kg/m<sup>2</sup>. Most women reported initiating breastfeeding ( $n = 536$ , 88%). At T1, 38% ( $n = 230$ ) of women reported breastfeeding their infant, whether partially or exclusively, for more than 6 months.

A subgroup of participants had data available on breastfeeding exclusivity ( $n = 165$ , 26%) at T1. Of these, 36% ( $n = 60$ ) exclusively breastfed their infant for less than 1 month, 27% ( $n = 44$ ) for 1 to 3 months, and 37% ( $n = 61$ ) for more than or equal to 4 months. Of the 160 women (97%) who attended the T2 visit, 28% ( $n = 135$ ) reported current breastfeeding.

#### 3.1 | Wheeze

Wheeze was reported for 40% ( $n = 246$ ) of infants at T1 and 52% ( $n = 261$ ) at T2. At T1, infants who were reportedly breastfed for more than 6 months had a 46% decreased risk of wheeze incidence (aRR 0.54, 95% CI, 0.30-0.96), relative to infants who were never breastfed (Figure 1). Breastfeeding duration (none, < 1 month, 1-3 months, 4-6 months, and > 6 months) was not significantly associated with wheeze incidence at T2 (Table 2). At T1, 12% ( $n = 78$ ) of infants were reported to have had a recurrent wheeze and 20% ( $n = 115$ ) at T2. Recurrent wheeze at T1 or T2 was not associated with breastfeeding duration (Table 2). The duration of exclusive breastfeeding was not associated with wheeze incidence at T1 or T2 (Table SI).

#### 3.2 | Bronchiolitis

Bronchiolitis was reported for 19% ( $n = 116$ ) of infants at T1 and 30% ( $n = 226$ ) at T2. There was a significant trend in the proportion of infants not breastfed who developed bronchiolitis ( $\chi^2$  trend analysis,  $P = .002$ , Table SII). Regression analysis showed a 52% reduced risk of bronchiolitis at T1 (aRR 0.48, 95% CI, 0.24-0.96) and a 55% reduced risk at T2 (aRR 0.45, 95% CI, 0.24-0.83) with more than 6 months of breastfeeding compared with never breastfeeding (Table 2).

#### 3.3 | Healthcare utilization

At T1, 9.6% ( $n = 58$ ) required an unscheduled GP visit, 11.7% ( $n = 71$ ) attended ED, 6.1% ( $n = 37$ ) were admitted to hospital, and 5.6% ( $n = 34$ ) were referred to a consultant in hospital. At T2, 22.4% ( $n = 109$ ) required an unscheduled GP visit, 14.6% ( $n = 71$ ) attended ED, 7.6% ( $n = 37$ ) were admitted to hospital, and 7% ( $n = 34$ ) were referred to a consultant in hospital.

**TABLE 1** Characteristics of mother-infant dyads (N = 605) from MAP/BLT longitudinal cohort studies

Maternal age at baseline <sup>a</sup> , y	29.8 ± 5.4
Maternal RCT group allocation during pregnancy	
Intervention arm	385 (63.0%)
Control arm	222 (37.0%)
Maternal BMI at baseline <sup>a</sup> , kg/m <sup>2</sup>	29.90 ± 8.1
Maternal BMI category at baseline, n (%)	
Underweight (<18.50 kg/m <sup>2</sup> )	20 (3.3%)
Healthy weight (18.51–24.99 kg/m <sup>2</sup> )	155 (26.0%)
Overweight (25–29.99 kg/m <sup>2</sup> )	178 (30.0%)
Obese Class I (30–34.99 kg/m <sup>2</sup> )	111 (18.7%)
Obese Class II (> 35 kg/m <sup>2</sup> )	132 (22.0%)
Ethnicity, n (%)	n = 544
European	418 (76.8%)
Aboriginal or Torres Strait Islander	33 (6.1%)
Mixed	52 (9.6%)
Asian	11 (2.0%)
Other	30 (11.0%)
Socio-Economic Indexes for Areas (SEIFA) quintiles, n (%)	
1st Quintile (lowest socioeconomic status)	76 (12.6%)
2nd Quintile	92 (15.2%)
3rd Quintile	244 (40.3%)
4th Quintile	160 (26.5%)
5th Quintile (highest socioeconomic status)	32 (5.4%)
Parental atopy, n (%)	
Maternal hayfever and/or eczema	540 (89.3%)
Paternal asthma	215 (37.0%)
Paternal hayfever and/or eczema	302 (53.0%)
Maternal age at completion of full time education	19.27 ± 3.9
<18, y, n (%)	116/601 (19.3%)
Gestational age at birth, wks	39.0 ± 2.1
Vaginal birth, n (%)	386/591 (65.3%)
Infant sex, male, n (%)	302/605 (49.8%)
Household pets, n (%)	308/605 (50.9%)
Siblings, n (%)	357/605 (58.7%)
Infant tobacco smoke exposure, n (%)	
In utero	80/597 (13.4%)
In infancy	150/591 (25.4%)
In utero and/or infancy	230/597 (38.5%)

Note: Data are presented as mean ± SD or n (%).

Abbreviations: BLT, Breathing for Life Trial; BMI, body mass index; MAP, Managing Asthma in Pregnancy; RCT, randomized controlled trial.

<sup>a</sup>(12–22 wks gestation).

Compared with never breastfeeding, breastfeeding for 4 to 6 months reduced the risk of wheeze-related ED presentation and hospital admission at T1 by 71% (aRR 0.29, 95% CI, 0.10–0.86) and 76% (aRR 0.24, 95% CI, 0.06–0.95), respectively (Table 2). Breastfeeding for more than 6 months also reduced the risk of ED

presentation (aRR 0.32, 95% CI, 0.14–0.76) and hospital admission at T1 (aRR 0.27, 95% CI, 0.10–0.76). Breastfeeding for more than 6 months (aRR 0.38, 95% CI, 0.19–0.78) and 1 to 3 months (aRR 0.44, 95% CI, 0.20–0.98) reduced unscheduled GP visits for asthma/wheeze symptoms at T2 compared with never breastfeeding.

### 3.4 | Medication use

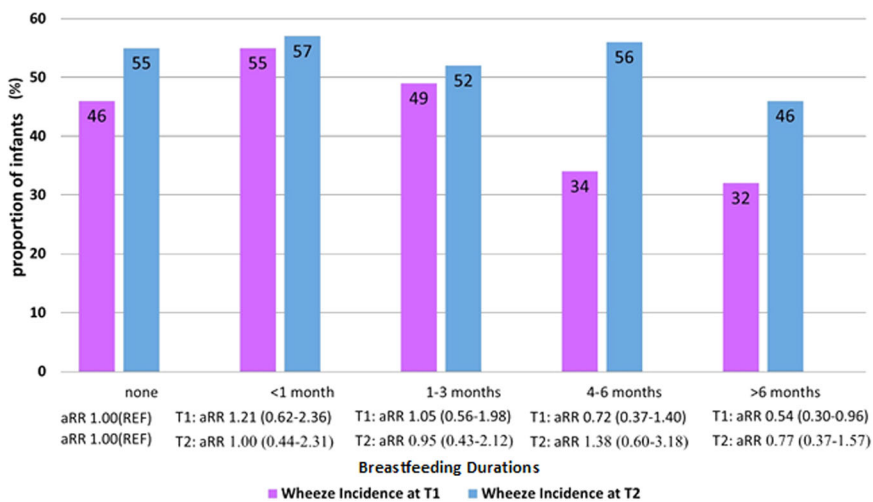
At T1, 6% (n = 36) reportedly received SABA, 2.5% (n = 15) received ICS, and 6.9% (n = 42) received OCS. At T2, 7.4% (n = 36) reportedly received SABA, 5.1% (n = 25) received ICS, and 20.2% (n = 98) received OCS.

There was no significant association between breastfeeding duration and the use of SABA, ICS, or OCS medications for asthma/wheeze symptoms at T1 or T2 (all  $P > .05$ ) (Table 2).

## 4 | DISCUSSION

In this secondary analysis of a cohort of infants born to women with asthma, breastfeeding for more than 6 months was associated with a reduced risk of infant wheeze and bronchiolitis, and fewer infants requiring medical attention compared with infants who were never breastfed. Breastfeeding for 4 to 6 months vs no breastfeeding also reduced healthcare utilization in the form of ED presentation and admission to hospital in these high-risk infants. However, the duration of exclusive breastfeeding was not associated with wheeze outcomes in subgroup analyses. Our results suggest that the duration of breastfeeding, regardless of exclusivity, may be an important factor in reducing the incidence and severity of wheeze, in infants at high-risk due to maternal asthma.

We observed a significant association between breastfeeding for more than 6 months and a lower relative risk of infant wheeze in this sample suggesting that continued exposure to breastfeeding may play an important role in preventing adverse respiratory outcomes. Breastfeeding for at least 1 month was also associated with a reduced risk of infant wheeze resulting in medical attention. In the general population, previous studies have reported a lower risk of adverse respiratory outcomes in offspring, including asthma, with both greater breastfeeding duration and exclusivity.<sup>18–20</sup> A recent study of n = 2773 infants found a 51% reduced risk of wheeze amongst those exclusively breastfed for 6 months compared with no breastfeeding (aRR 0.49, 95% CI, 0.49–0.84).<sup>21</sup> However, when the analysis was stratified, this association was confined to infants whose mothers had asthma ( $P = .001$ ),<sup>21</sup> with a 62% reduced risk of wheeze in the first year of life (aRR 0.38, 95% CI, 0.20–0.71). This effect was also observed after 12 months of any breastfeeding (aRR 0.52, 95% CI, 0.35–0.77) but not 6 to less than 12 months, relative to less than 6 months of any breastfeeding. This may suggest that longer breastfeeding duration could reduce the risk of wheeze in early life. The lack of a significant association between breastfeeding exclusivity and wheeze-related outcomes in our study may have been due to the smaller sample size in these analyses. Therefore, further



**FIGURE 1** The association between breastfeeding duration and risk of wheeze ever at 6 months and 12 months of age in infants born to women with asthma. Legend shows aRR, adjusted relative risk with 95% confidence interval presented, adjusted for maternal age, maternal BMI, maternal age at completion of full time education, mode of birth, socioeconomic status (SEIFA), and smoke exposure. T1, 6 ± 1 months; T2, 12 ± 1 months. BMI, body mass index [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

investigation into the role of breastfeeding exclusivity in respiratory health in infants exposed to maternal asthma is warranted.

In our cohort, breastfeeding for more than 6 months provided a protective effect on parent-reported bronchiolitis throughout infancy. Breastfeeding for more than or equal to 4 to 6 months and more than 6 months was associated with a reduced risk of ED

attendance and admission to hospital, compared with no breastfeeding, with breastfeeding for 1 to 3 months and more than 6 months also associated with a reduced risk of unscheduled GP visits. This indicates that longer duration breastfeeding impacts on the incidence of wheeze, with shorter durations impacting on the severity of wheeze, potentially decreasing the need for healthcare

**TABLE 2** Multinomial logistic regression models for breastfeeding duration and infant respiratory outcomes, related medication use, and healthcare utilization at 6 months and 12 months of age

Secondary outcomes	Exposure: breastfeeding duration in months aRR* (95% CI)				
	0 mo (n = 75)	< 1 mo (n = 86)	1-3 mo (n = 113)	4-6 mo (n = 101)	> 6 mo (n = 230)
Infant respiratory outcomes at T1 (6 ± 1 mo)					
Recurrent wheeze	1.00 (REF)	0.78 (0.27-2.26)	1.28 (0.51-3.21)	0.71 (0.24-2.09)	0.79 (0.32-1.99)
Bronchiolitis ever	1.00 (REF)	0.84 (0.39-1.82)	0.70 (0.33-1.45)	0.61 (0.28-1.36)	<b>0.48 (0.24-0.96)</b>
Presentation to ED for wheeze	1.00 (REF)	0.73 (0.33-1.77)	0.93 (0.42-2.10)	<b>0.29 (0.10-0.86)</b>	<b>0.32 (0.14-0.76)</b>
Admission to hospital for wheeze	1.00 (REF)	0.58 (0.21-1.59)	0.58 (0.29-1.59)	<b>0.24 (0.06-0.95)</b>	<b>0.27 (0.10-0.76)</b>
Referral to consultant for wheeze	1.00 (REF)	0.64 (0.16-2.50)	1.84 (0.62-5.40)	0.42 (0.08-2.23)	0.67 (0.20-2.24)
Unscheduled GP visit for wheeze	1.00 (REF)	0.85 (0.26-2.74)	0.81 (0.25-2.57)	1.63 (0.55-4.78)	1.09 (0.40-2.99)
SABA use for wheeze	1.00 (REF)	0.65 (0.19-2.21)	0.87 (0.30-2.57)	0.52 (0.14-1.93)	0.49 (0.16-1.47)
ICS use for wheeze	1.00 (REF)	0.60 (0.09-3.85)	1.02 (0.21-4.88)	0.96 (0.17-5.38)	0.31 (0.05-2.12)
OCS use for wheeze	1.00 (REF)	1.20 (0.40-3.56)	0.69 (0.20-2.39)	0.66 (0.19-2.27)	0.46 (0.15-1.44)
Infant respiratory outcomes at T2 (12 ± 1 mo)					
Recurrent wheeze	1.00 (REF)	0.89 (0.35-2.22)	1.26 (0.53-3.01)	0.97 (0.37-2.58)	0.75 (0.32-1.76)
Bronchiolitis ever	1.00 (REF)	1.20 (0.63-2.30)	0.78 (0.41-1.51)	1.09 (0.55-2.17)	<b>0.45 (0.24-0.83)</b>
Presentation to ED for wheeze	1.00 (REF)	2.22 (0.87-5.72)	1.22 (0.46-3.19)	0.59 (0.17-1.93)	0.61 (0.23-1.62)
Admission to hospital for wheeze	1.00 (REF)	2.12 (0.65-6.95)	0.91 (0.25-3.25)	0.73 (0.18-3.00)	0.57 (0.17-1.95)
Referral to consultant for wheeze	1.00 (REF)	1.35 (0.38-4.75)	1.93 (0.60-6.25)	0.26 (0.03-2.36)	0.79 (0.22-2.86)
Unscheduled GP visit for wheeze	1.00 (REF)	0.60 (0.28-1.29)	<b>0.44 (0.20-0.98)</b>	0.55 (0.24-1.24)	<b>0.38 (0.19-0.78)</b>
SABA use for wheeze	1.00 (REF)	1.79 (0.26-2.39)	1.26 (0.46-3.45)	2.06 (0.75-5.63)	0.88 (0.35-2.22)
ICS use for wheeze	1.00 (REF)	0.83 (0.20-3.54)	0.57 (0.12-2.68)	1.05 (0.24-4.59)	0.60 (0.15-2.45)
OCS use for wheeze	1.00 (REF)	1.02 (0.43-2.43)	1.14 (0.50-2.60)	0.82 (0.32-2.08)	0.80 (0.36-1.77)

Note: Bold font indicates significant result.

Abbreviations: aRR, adjusted relative risk; BMI, body mass index; CI, confidence interval; ED, emergency department; GP, general practitioner; ICS, inhaled corticosteroid; OCS, oral corticosteroid; SABA, short acting beta-agonists.

\*Adjusted for maternal age, maternal BMI, maternal age at completion of full-time education, mode of birth, socioeconomic status (SEIFA), and smoke exposure.



intervention in infants at high risk due to maternal asthma. Indeed, presenting to ED was much more common than an unscheduled GP consultation in the never breastfed group (21% vs 9%) indicating that parents required more urgent assistance for their infants' wheeze; yet, the medication use (SABA, ICS, and OCS) was not associated with breastfeeding duration in our cohort. Although parent-reported bronchiolitis incidence and wheeze incidence were high in our cohort, the reported use of respiratory medications was relatively low, which may explain the lack of significance for medication use. Therefore, larger cohorts are needed to explore this outcome.

The protective effect of breastfeeding seen in early life may be via exposure to the immunological components of breastmilk and subsequent passive immunity offering protection against respiratory tract infections—a major cause of infant wheeze.<sup>12,13</sup> This protection may be tapered or lost as breastfeeding is reduced or discontinued. Indeed, Wright et al<sup>30</sup> ( $n = 1246$ ) found that breastfeeding was protective against poor respiratory outcomes in the first 2 years of life (OR, 0.45, 95% CI, 0.2–0.9), regardless of the presence of maternal asthma. However, increased exposure to breastfeeding (exclusive breastfeeding for  $\geq 4$  months) in the presence of maternal asthma was associated with a significantly increased odds of developing asthma at 6 years (OR, 8.7, 95% CI, 3.4–22.2), and higher odds of recurrent wheeze at age 6 to 13 years (OR, 5.7, 95% CI, 2.3–14.1), compared with children of non-asthmatic mothers who were not exclusively breastfed for more than or equal to 4 months.<sup>30</sup> A recent review has shown the odds of developing asthma or wheeze in children exposed to maternal asthma to be three-fold higher than those not exposed to maternal asthma (OR, 3.04, 95% CI, 2.59–3.56)<sup>3</sup> which is consistent with the lower end of Wright's CIs for asthma and wheeze in childhood in the maternal asthma group. These data suggest that infants exposed to maternal asthma are at high risk of adverse respiratory health, compared with those not exposed to maternal asthma in utero, and that there is an interaction with atopy development. Alternatively, it is possible that reverse causation contributes to the positive associations between breastfeeding and adverse respiratory outcomes. The duration of breastfeeding could be influenced by the mothers' asthma status and/or early signs or symptoms of atopy/wheeze in the child, as an attempt to prevent further manifestation. Lowe et al<sup>31</sup> ( $n = 620$ ) found that early signs of atopy (inclusive of symptoms of asthma) were independently associated with a ~30% reduction in the risk of ceasing exclusive breastfeeding. This suggests that infants who exhibited signs of atopy were more likely to be breastfed exclusively for a longer period of time than infants that did not show early signs of atopy. However, information on early atopic characteristics of the infant was not examined in our cohort, such as skin prick tests or GP diagnosis; thus, we were unable to examine whether this variable impacted on the observed associations between breastfeeding patterns and wheeze incidence and severity. Further exploration into factors associated with infant and child feeding patterns and measurements of atopy is warranted.

Although a validated questionnaire was used,<sup>23</sup> the use of parent report to identify offspring respiratory outcomes (and breastfeeding duration) may be subject to retrospective recall bias. Categorical reporting of breastfeeding duration in the questionnaire, as opposed to a continuous measure of this variable, may also have limited our power to

detect an association with infant wheeze. Furthermore, this was a secondary analysis of data from two RCTs, which were not originally designed to answer the outcomes of interest in this paper. Some strengths include longitudinal follow-up of participants, relatively large sample size and use of a well-defined population of mothers with asthma and their infants, examination of wheeze severity outcomes, consideration of key confounders, and assessment of breastfeeding duration and intensity (measured by exclusivity). Future work would benefit from more detailed information on breastfeeding duration and exclusivity, ideally with a standardized validated breastfeeding tool; exploration of potential mechanisms by which breastfeeding may support optimal infant respiratory development; and objective measurement of infant respiratory outcomes, including confirmation of respiratory tract infection to investigate possible mechanisms of action.

In this study of infants at high risk of adverse respiratory outcomes due to maternal asthma, we observed a reduced risk of wheeze and bronchiolitis incidence with more than 6 months of breastfeeding and a reduced risk of wheeze-related healthcare utilization with more than or equal to 1 month of breastfeeding. This supports the evidence base that breastfeeding may be beneficial to infant respiratory health, particularly for infants at increased risk due to maternal asthma. Our results suggest that supporting women with asthma to breastfeed for at least 6 months could potentially reduce the risk of wheeze in their infants, with breastfeeding for at least 1 month reducing related healthcare utilization.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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