

ORIGINAL ARTICLE

Protective effect of breastfeeding on recurrent cough in adulthood

Kimberly D Gerhart,^{1,2} Debra A Stern, Stefano Guerra,¹ Wayne J Morgan,^{1,3} Fernando D Martinez,¹ Anne L Wright^{1,2}

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2017-210841>).

¹Asthma and Airway Disease Research Center UAHS, University of Arizona, Tucson, Arizona, USA

²Department of Pediatrics, University of Arizona, Tucson, Arizona, USA

³Pediatric Pulmonary Allergy Division, University of Arizona, Tucson, Arizona, USA

Correspondence to

Dr Anne L Wright, Pediatrics and the Asthma and Airway Disease Research Center, University of Arizona College of Medicine, Tucson, AZ 85724, USA; wrightal@email.arizona.edu

Received 1 August 2017
Revised 11 April 2018
Accepted 23 April 2018
Published Online First
21 May 2018

ABSTRACT

Rationale Breastfeeding protects from respiratory infections in early life but its relationship to recurrent cough and other respiratory outcomes in adult life is not well established.

Methods Infant feeding practices were assessed prospectively in the Tucson Children's Respiratory Study, a non-selected birth cohort and categorised into formula from birth or introduced <1 month, formula introduced ≥1 to <4 months and exclusive breastfeeding for ≥4 months. Infant feeding was assessed as an ordinal variable representing an increasing dose of breastmilk across the three categories. *Recurrent cough* was defined at 22, 26 and 32 years as ≥2 episodes of cough without a cold lasting 1 week during the past year. Covariates included participant sex, race/ethnicity and smoking as well as parental smoking, education, age and asthma. Covariates were evaluated as potential confounders for the relation between infant feeding and adult outcomes.

Results Of the 786 participants, 19% breastfed <1 month, 50% breastfed ≥1 to <4 months and 31% breastfed ≥4 months. The prevalence of recurrent cough at 22, 26 and 32 years was 17%, 15% and 16%, respectively. Each ordinal increase in breastfeeding duration was associated with a decreased risk of recurrent cough in adult life: adjusted OR=0.71, (95% CI: 0.56 to 0.89), p=0.004. Additional adjustment for concurrent adult asthma, wheeze, smoking and lung volume did not change these results.

Conclusion Longer duration of breastfeeding reduces the risk of recurrent cough in adult life, regardless of smoking and other respiratory symptoms, suggesting long-term protective effects on respiratory health.

INTRODUCTION

There is a large body of literature which considers the relation of infant feeding and respiratory symptoms in infancy, with most studies indicating that breastfeeding has a protective effect. Multiple studies have shown that longer duration of breastfeeding is associated with reduced prevalence of wheeze in infancy.^{1,2} A Dutch study³ showed that breastfeeding was associated in a dose relation with decreased risk of dry cough in the first 4 months of life, as well as wheezing, shortness of breath and persistent phlegm. Others² have shown that the severity of lower respiratory illnesses (LRIs) in infancy was reduced with exclusive breastfeeding, and LRIs that occurred among breastfed infants were of shorter duration. A large meta-analysis of infant feeding and health outcomes⁴ showed lower

Key messages**What is the key question?**

- Does breastfeeding protect from respiratory symptoms in adult life?

What is the bottom line?

- Longer duration of breastfeeding reduces the risk of recurrent cough in adult life, regardless of smoking and other respiratory symptoms, suggesting long-term protective effects on respiratory health.

Why read on?

- To discover how infant feeding choices can have an impact on respiratory health in adult life.

ORs for cough and wheeze associated with breastfeeding in a dose–response pattern.

Whether breastfeeding provides similar protection against respiratory symptoms in later life is less well established. Despite showing a dose–response relation of breastfeeding to wheeze in the first 3 years of life, Elliott *et al*⁵ found no significant association by age 7–8 in the large Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. In a longitudinal follow-up of children aged 9–26 years, Sears⁶ found no evidence that breastfeeding protected against asthma. Similarly, in following a birth cohort of 1314 newborns up to age 20 in five German cities, Grabenhenrich *et al*⁷ showed no association between breastfeeding and asthma. However, given that both wheeze and cough in early life are associated with later respiratory symptoms,⁸ it is possible that infant feeding practices may be associated with respiratory symptoms in adult life in the absence of a diagnosis of asthma.

Our aim was to determine if infant feeding patterns are associated with respiratory outcomes in adult life using data from the Tucson Children's Respiratory Study, a large non-selected birth cohort in which infant feeding practices and adult health outcomes were ascertained prospectively. The population has been followed longitudinally to age 32, with questionnaires regarding cough, wheeze and asthma completed multiple times in adult life. We hypothesise that a longer duration of breastfeeding has a protective effect against respiratory symptoms in adult life.



► <http://dx.doi.org/10.1136/thoraxjnl-2018-211871>



To cite: Gerhart KD, Stern DA, Guerra S, *et al*. *Thorax* 2018;**73**:833–839.

METHODS

Study design

Healthy infants were enrolled at birth in the Tucson Children's Respiratory Study between 1980 and 1984 (n=1246).⁹ At enrolment, parents completed a questionnaire describing their race and ethnicity, history of physician-diagnosed asthma, years of education, current age and current smoking habits. *Participant* race and ethnicity were determined from this parental information and categorised as 'non-Hispanic White' (both parents), 'Hispanic White' (one or both parents) and all other race/ethnic groups combined into 'Other' (African American, Asian American, Native American and other). Parental education was defined as ≤ 12 years of education compared with > 12 years of education, parental asthma as a report of physician-diagnosed asthma, parental smoking as actively smoking at the time of the child's birth and parental age as ≤ 28 years old compared with > 28 years old.

Infant feeding practices

Feeding practices were assessed prospectively based on forms completed by the child's paediatrician at well-child visits at ages 2, 4, 6 and 9 months. Infant feeding was categorised into three groups as described previously¹⁰: formula provided from birth or introduced < 1 month ('Breastfed < 1 month'), formula and/or food introduced between ≥ 1 to < 4 months ('Breastfed ≥ 1 to < 4 months') and exclusive breastfeeding for four or more months ('Exclusive breastfed ≥ 4 months').

Adult assessments

Questionnaires were completed at 22, 26 and 32 years of age. *Recurrent cough* was defined as two or more episodes of cough without a cold that lasted 1 week during the past year as previously reported for participants in this cohort.^{11 12} For recurrent cough, one episode of cough without a cold during the past year was combined with no cough group. A summary measure of the prevalence of adult recurrent cough between 22 and 32 years of age ('Recurrent cough 22–32') was defined as any report of recurrent cough at any adult age.

Active wheeze was defined as one or more episodes during the past year and active physician-diagnosed asthma as a report of a physician diagnosis of asthma and reported symptoms (asthma episodes or attacks and/or wheeze) during the past year. Active smoking was defined as any smoking in the past year, heart burn (acid or gastro-oesophageal reflux) as at least one reported episode during the past year, sinus trouble as a report of a physician diagnosis of sinus trouble with one or more episodes during the past year¹¹ and allergic rhinitis as hay fever or runny, stuffy nose that a doctor said was allergic in nature. Adult body mass index (BMI) was calculated from self-reported height and weight at each age.

Lung volumes

Because we had previously found that longer duration of breastfeeding was associated with better FVC in childhood,¹⁰ we considered lung volume as a potential confounder. The FVC was determined from pulmonary function tests obtained at each adult age as described previously.¹³

Early life factors

Multiple early life factors were considered for their relations to infant feeding and recurrent cough as potential confounders. Respiratory syncytial virus (RSV) LRIs were identified from viral cultures of nasopharyngeal swabs and throat specimens collected

during the acute phase of the illness as previously described.¹⁴ Cold air bronchial hyper-responsiveness (BHR) was measured at age 6 as previously defined.¹⁵ Early wheezing phenotypes were previously described as persistent wheezing (wheeze during lower respiratory tract illness before 3 years and wheeze at 6 years), late-onset wheezing (wheeze only at 6 years), transient early wheezing (wheeze only during lower respiratory tract illness before 3 years) and never wheezing.¹⁶ Atopy was defined as a positive skin-prick test to at least one of seven local aeroallergens (Bermuda grass, *Alternaria alternata*, careless weed, house-dust mix and mesquite, mulberry and olive-tree pollens).¹⁷

Statistical analysis

Infant feeding was evaluated as an ordinal variable (0, 1, 2) and as a categorical variable with the breastfed < 1 month group considered as the reference group using logistic regression. The ordinal variable had a lower Akaike's information criteria compared with the categorical infant feeding variable, so the first was used in all models as representing increasing duration of breastfeeding. Relations between breastfeeding duration and covariates or adult respiratory outcomes were assessed using contingency tables and the X^2 statistic. A Mantel-Haenszel test of trend was computed for the unadjusted age-specific relation between breastfeeding duration and respiratory outcomes (IBM SPSS Statistics 24). ORs for each respiratory outcome were determined after adjustment using logistic regression. The generalised estimating equation, using an exchangeable correlation structure, was used to longitudinally assess the relation between breastfeeding duration and adult recurrent cough, asthma and wheeze (STATA 14). Models were adjusted for sex, race/ethnicity and parental smoking, education, age and asthma as fixed covariates and participant active smoking as a time-dependent covariate. This research was approved by the Institutional Review Board of the University of Arizona and informed consent/assent was obtained from/for all participants.

RESULTS

Of the 1246 participants enrolled at birth, those with information for infant feeding and who completed one or more adult questionnaire were included in the current analysis (n=786). Of these, 503 completed all three questionnaires, 163 completed two questionnaires and 120 completed one questionnaire. Included participants (n=786) were more likely to have non-smoking parents with more years of education and to be non-Hispanic White, compared with those excluded from the current analysis because of missing data (n=460; online supplementary Etable 1). Parental history of asthma was similar for both groups.

Infant feeding

Formula was introduced at birth or < 1 month for 19.2% of the participants (n=151) and between ≥ 1 to < 4 months for 49.6% of the participants (n=390), while 31.3% were exclusively breastfed ≥ 4 months (n=245) (table 1). Non-Hispanic White, non-smoking parents with more years of education were more likely to exclusively breastfeed ≥ 4 months (table 1). However, there was no relation between parental asthma and infant feeding choice (table 1).

Adult respiratory outcomes

The prevalence of recurrent cough, that is, two or more episodes of cough without a cold lasting 1 week during the past year, was similar at the three adult ages: 16.7% at 22 years, 14.7% at 26 years and 16.0% at 32 years, and the overall prevalence

Table 1 Demographic characteristics of the infant feeding groups

Characteristic	Category	Breastfed						P values
		<1 month		≥1 to <4 months		≥4 months		
		%	n	%	n	%	n	
Sex	All	19.2	151	49.6	390	31.2	245	–
	Male	44.4	67	45.9	179	50.6	124	
	Female	55.6	84	54.1	211	49.4	121	0.389
Race/ethnicity	Non-Hispanic White	55.0	83	60.0	234	79.2	194	
	Hispanic White	26.5	40	26.9	105	13.1	32	
	Other	18.5	28	13.1	51	7.8	19	<0.001
Maternal								
Asthma	No	94.6	141	88.2	337	87.7	214	
	Yes	5.4	8	11.8	45	12.3	30	0.063
Smoking	No	78.8	119	84.1	328	90.6	222	
	Yes	21.2	32	15.9	62	9.4	23	0.004
Education	≤12 years	43.1	65	23.6	92	13.1	32	
	>12 years	57.0	86	76.4	297	86.9	213	<0.001
Age	≤28 years	62.3	94	62.6	244	53.9	132	
	>28 years	37.7	57	37.4	146	46.1	113	0.075
Paternal								
Asthma	No	83.3	115	87.4	320	89.1	213	
	Yes	16.7	23	12.6	46	10.9	26	0.265
Smoking	No	60.1	89	72.4	278	80.0	196	
	Yes	39.9	59	27.6	106	20.0	49	<0.001
Education	≤12 years	37.2	54	23.0	88	14.3	35	
	>12 years	62.8	91	77.0	294	85.7	210	<0.001
Age	≤28 years	46.0	68	46.0	174	34.3	84	
	>28 years	54.0	80	54.0	208	65.7	161	0.012

Proportions compared by χ^2 .

of adult recurrent cough reported between ages 22 and 32 was 28.4% (223/786) (online supplementary Etable 2). Of the participants who completed all three adult questionnaires (n=503), 165 reported recurrent cough at one or more times: 9.7% (n=16) at all three ages, 23.6% (n=39) at two ages and 66.7% (n=110) at one age. Of the socioeconomic or parental factors tested for potential confounding, only paternal asthma was associated with an increased risk of recurrent cough at age 22, but not at ages 26

or 32 (online supplementary Etable 2). Early life risk factors for asthma, such as RSV LRI¹⁴ and persistent wheeze,¹⁶ were unrelated to recurrent cough in adult life (online supplementary Etable 3). Further, factors commonly associated with asthma such as cold air BHR and atopy at age 6 showed no consistent relation to recurrent cough (online supplementary Etable 3).

In adult life, participants who reported either recurrent cough or active wheeze were more likely to smoke compared with those

Table 2 Prevalence of active smoking at ages 22, 26 and 32 years by concurrent respiratory symptoms

Active adult respiratory symptoms	Concurrent adult smoking								
	22 years			26 years			32 years		
	N	%+	P values	N	%+	P values	N	%+	P values
Recurrent cough									
No	593	22.9		557	21.0		494	12.2	
Yes	119	38.7	<0.001	95	32.6	0.012	94	30.9	<0.001
Wheeze									
No	439	18.5		397	18.4		391	10.7	
Yes	278	37.1	<0.001	256	29.3	0.001	205	24.9	<0.001
MD asthma									
No	580	24.7		518	22.0		483	14.9	
Yes	134	29.9	0.2	130	24.6	0.5	113	18.6	0.3

Proportions compared by χ^2 .
MD, physician diagnosed.

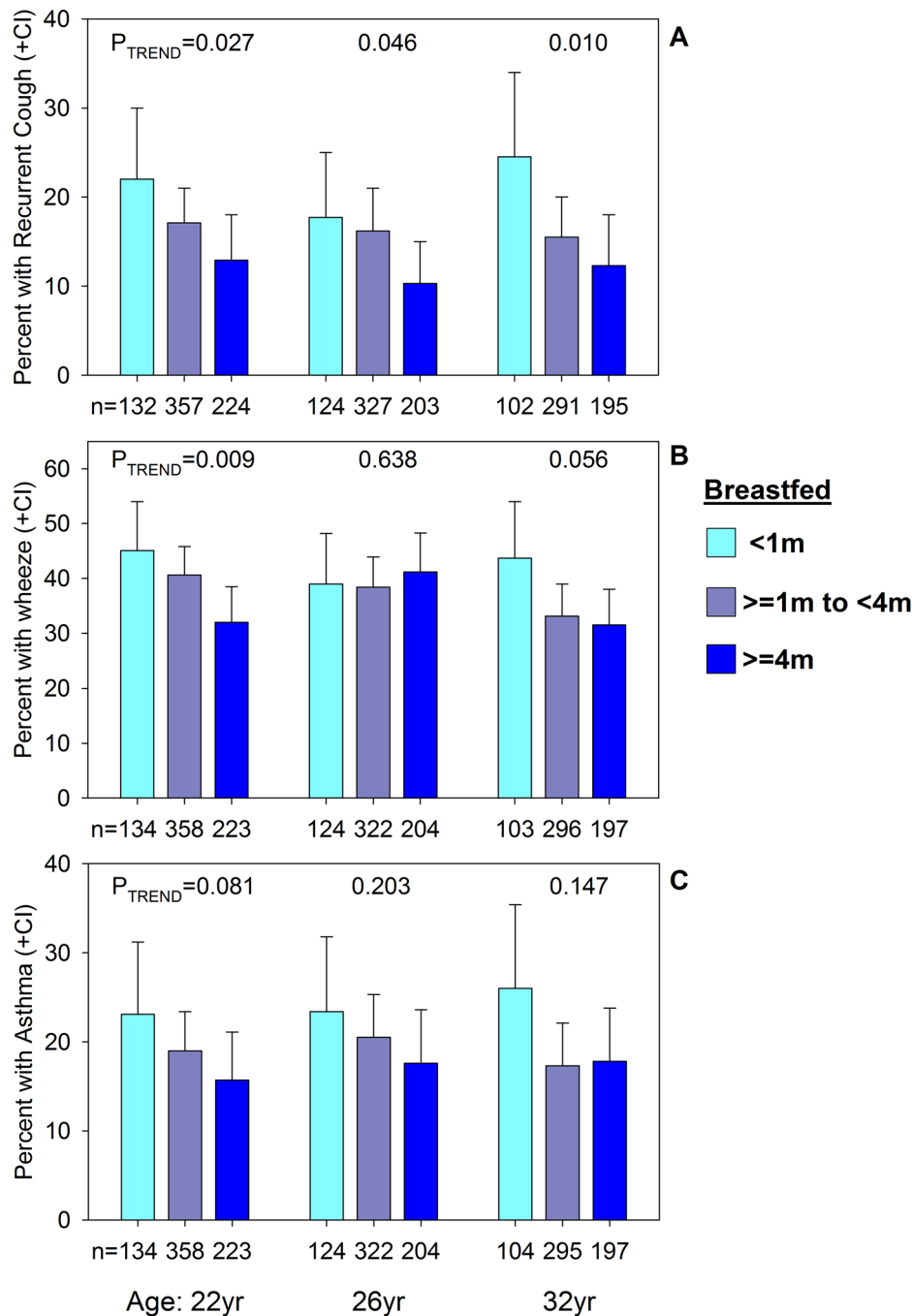


Figure 1 Association of infant feeding and adult recurrent cough (A), wheeze (B) and asthma (C) at ages 22, 26 and 32 years; proportions compared across the ordinal infant feeding categories using a Mantel-Haenszel test of trend.

without such symptoms (table 2). In contrast, adult asthma was unrelated to concurrent smoking. Recurrent cough was associated with active wheeze and asthma at each age (online supplementary Etable 4). In addition, adults with recurrent cough reported rhinitis, sinus trouble and heart burn more often than those without recurrent cough (online supplementary Etable 4). There was no relation between recurrent cough and concurrent BMI at 22, 26 or 32 (data not shown).

Infant feeding and recurrent cough

In unadjusted *age-specific* analyses (figure 1), there was a significant protective effect for increasing duration of breastfeeding

on recurrent cough at all three adult ages. The same effect was also evident for wheeze at age 22, but not at ages 26 or 32 years. No statistically significant association was observed between infant feeding considered as an ordinal variable representing an increasing breastfeeding duration and active adult asthma. At age 22, those in the early formula group were more likely to smoke compared with those with more breastfeeding (online supplementary Etable 5). However, by ages 26 and 32, infant feeding showed no relation to active adult smoking.

After adjusting for sex, race/ethnicity and current smoking as well as maternal and paternal smoking, education, age and asthma in *age-specific* models, a similar protective effect for increasing

duration of breastfeeding on recurrent cough was present at all ages. For each ordinal increase in breastfeeding duration, there was a corresponding decreased risk of recurrent cough in adult life at age 22 (adjusted OR (aOR)=0.72, (95% CI: 0.52 to 1.00); $p=0.049$, $n=668$) and age 32 (aOR=0.65, (95% CI: 0.44 to 0.94); $p=0.021$, $n=549$). At age 26, there was a similar trend, though it was not statistically significant (aOR=0.75, (95% CI: 0.53 to 1.06); $p=0.108$, $n=611$) (full models shown in online supplementary Etable 6).

Longitudinal models were used to assess the relation of breastfeeding duration to recurrent cough over the 22–32 age span. There was a significant protective relation between breastfeeding duration and recurrent cough between ages 22 and 32 (aOR=0.71, (95% CI: 0.56 to 0.89); $p=0.004$, 735 subjects, 1828 observations) after adjusting for sex, race/ethnicity, active current smoking as well as parental smoking, education, age and asthma (online supplementary Etable 6). Additional adjustment of this basic model for the relation between breastfeeding duration and recurrent cough with concurrent adult asthma, wheeze and lung volume (FVC) did not appreciably change the results (aOR=0.69, (95% CI: 0.50 to 0.94); $p=0.019$, 560 subjects, 1122 observations). Further adjustment of this basic model with concurrent BMI did not change the results (aOR=0.68, (95% CI: 0.54 to 0.86); $p=0.002$, 732 subjects, 1769 observations). There was no statistically significant relation between breastfeeding duration considered as an ordinal variable and adult wheeze (aOR=0.89, (95% CI: 0.73 to 1.07); $p=0.203$) or asthma (aOR=0.86, (95% CI: 0.66 to 1.12); $p=0.267$) between ages 22 and 32 years in adjusted longitudinal models.

There were no significant interactions between breastfeeding duration and the main covariates: sex, race/ethnicity, active current smoking and parental smoking, education, age and asthma (data not shown). There were also no interactions between breastfeeding duration and the early life risk factors: RSV, wheezing phenotypes, cold air hyper-responsiveness or atopy (data not shown).

DISCUSSION

This analysis demonstrates that a longer duration of breastfeeding is associated with lower prevalence of recurrent cough in adulthood 22–32 years later. While wheeze at age 22 was also reduced in association with longer breastfeeding, this relationship did not account for the significant relation with recurrent cough. The relation between feeding and recurrent cough could not be attributed to group differences between those who did and did not breastfeed exclusively as these differences were controlled in analyses.

There is significant evidence that breastfeeding is associated with reduced acute respiratory symptoms in infancy and early childhood. In addition to studies which show a reduced prevalence of cough³ and/or wheeze in infancy^{1–2} associated with breastfeeding, there is evidence of reduced respiratory symptoms into the preschool years. A Finnish study¹⁸ showed a dose–response relation between duration of exclusive breastfeeding and persistent cough up to 7–9 months, although adjusted odds for cough increased with increasing breastfeeding after that age, suggesting the presence of unmeasured confounders. Sucharew *et al*¹⁹ showed that recurrent night cough to age 3 was less common among breastfed children, although when wheezing was included in the model the relation with breastfeeding became non-significant. We have previously shown in this same cohort that

longer duration of breastfeeding is associated with reduced prevalence of wheeze to age 6 years among non-atopic children.²⁰ However, to our knowledge, there has been no previous report of an association of infant feeding and prevalence of cough or other respiratory symptoms in adult life independent of a diagnosis of asthma.

Whether breastfeeding reduces risk for asthma is controversial. Although a meta-analysis found that exclusive breastfeeding was associated with a lower risk of asthma between ages 2 and 5²¹, we, and others, have shown prospectively that the relation to asthma in late childhood is far from simple and that maternal characteristics may alter the effect.^{14–22} In the current analysis, subjects with recurrent cough are more likely to report wheeze, asthma, rhinitis, sinusitis and heart burn. However, they are no more likely to be atopic than subjects without recurrent cough consistent with our earlier observations about recurrent cough without wheeze in childhood.¹² Further, the relation with recurrent cough was independent of asthma, and adjusting for the other conditions did not change the relationship observed. This suggests that adult recurrent cough is not cough-variant asthma but rather a different phenotype, potentially the tip of the iceberg for later respiratory morbidity.

Cough is common in childhood⁸ and typically occurs in association with acute respiratory infections. Although this symptom has received little attention relative to wheeze, we have recently shown that recurrent cough in infancy is a risk factor for subsequent asthma.⁸ In adult life, however, recurrent cough may be an early manifestation of airway obstruction. In the older National Health and Nutrition Examination Survey population,²³ individuals with recurrent cough, defined as ‘usual cough on most days for 3 consecutive months or more during the past year,’ were more likely have moderate to severe obstruction and to report fair/poor health than those with no symptoms. Symptomatic mild obstruction is associated with a faster decline in FEV₁ and greater utilisation of healthcare services for respiratory outcomes²⁴ relative to subjects without symptomatic mild obstruction. These results suggest that chronic respiratory symptoms in adulthood may be risk factors for both morbidity and poor quality of life even in the absence of a diagnosis, thereby warranting research into their early life predictors. Recurrent cough is also associated with cigarette smoking²⁵ that often precedes development of airflow obstruction.²⁶ In our study, although smoking was more common among subjects with recurrent cough, adjusting for smoking did not alter the relation with breastfeeding.

There may be several possible biological explanations for the association of infant feeding practices with recurrent cough in adult life. First, it is possible that early respiratory illnesses increase risk for later respiratory symptoms, and the protective effect of breastfeeding on the former may reduce the risk for the latter. In this cohort, however, neither early wheezing LRIs nor RSV LRIs were associated with recurrent cough in adult life, indicating that they cannot account for the relation of infant feeding to adult cough. Second, it has been shown that some components of human milk are associated with epigenetic changes in infancy, but the mechanisms involved are still unclear²⁷ and any link between epigenetic changes and subsequent risk for cough or other respiratory symptoms in adult life remains to be elucidated. Other studies have suggested that the use of a bottle, particularly for feeding in the crib prior to sleep,²⁸ regardless of content, may be as important as what is in the bottle in conferring risk for cough and wheezing in infancy. Soto-Ramirez *et*

*al*²⁹ showed that infants who are exposed to the bottle, even when they are receiving human milk, are more likely to experience cough and wheeze in infancy, suggesting that bottle feeding may result in regurgitation and aspiration, which could lead to increased mucous production in the airways. While we do not have data on Tucson Children's Respiratory Study subjects as to whether exclusively breastfed infants were ever fed with a bottle, there was no relation of early cough with later recurrent cough. Finally, breastfeeding has been shown to bear a relation with subsequent lung function, with some studies documenting larger lung volumes in adolescence^{10 30} as well as an increased FEV₁/FVC³¹ associated with breastfeeding. Adjusting our models for lung volume did not alter the results. Although the mechanism for the observed relation is unclear, studies have shown a relation of infant feeding practices to other adult health outcomes such as Crohn's disease or metabolic syndrome, providing support that such a long-term effect is plausible.^{32–35}

This analysis has several potential limitations. First, there are multiple differences between mothers who breastfeed and those who do not. While we adjusted for key factors such as education and age, there may be other unmeasured differences that could have contributed to the observed effect. Second, the results relied on self-report of symptoms in adult life, which may be affected by reporting bias associated with asthma; however, the relation persisted when asthma was included as a potential confounder in multivariate analyses. Third, subjects with recurrent cough were also more likely to have other symptoms and diagnoses, raising the possibility that the effect is not specific to recurrent cough. Adjusting for these other symptoms did not alter the results. In addition, study participants who were breastfed for longer were more likely to still be participating in the study at age 32 (80%) compared with those breastfed for the intermediate (75%) and shortest duration (68%). However, the proportions responding at ages 22 and 26 were roughly comparable between the high and low breastfeeding groups, and the trends with recurrent cough are in the same direction and of comparable magnitude at all ages. Strengths of the study include the prospective assessment of infant feeding practices, the high participation rate, the consistency of findings across the adult ages and the extensive follow-up of this non-selected population.

In conclusion, this analysis documents a protective relation between breastfeeding in early life and recurrent cough at ages 22–32. Longer duration of breastfeeding is associated with a dose-related reduced prevalence of adult recurrent cough, suggesting potential long-term protective effects on respiratory health. Future research should consider relations of breastfeeding with adult symptoms and conditions, to ascertain whether this behaviour in early life is associated with alterations in adult health beyond the protection it provides in infancy.

Contributors Study concept and design: FDM, ALW, DAS and KDG; participant recruitment: ALW; acquisition of data: ALW, FDM and WJM; analysis of data: DAS, KDG, SG, WJM and FDM; data interpretation and drafting of the manuscript: KDG, DAS, SG, WJM, ALW and FDM. All authors critically read, commented on and approved the final version of the manuscript.

Funding This work was supported by US Department of Health and Human Services, National Institutes of Health, National Heart Blood and Lung Institute grant number 132523.

Competing interests None declared.

Patient consent Not required.

Ethics approval This research was approved by the institutional review board of the University of Arizona.

Provenance and peer review Not commissioned; externally peer reviewed.

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Wright AL, Holberg CJ, Martinez FD, *et al*. Breast feeding and lower respiratory tract illness in the first year of life. Group Health Medical Associates. *BMJ* 1989;299:946–9.
- 2 Cushing AH, Samet JM, Lambert WE, *et al*. Breastfeeding reduces risk of respiratory illness in infants. *Am J Epidemiol* 1998;147:863–70.
- 3 Sonnenschein-van der Voort AM, Jaddoe VW, van der Valk RJ, *et al*. Duration and exclusiveness of breastfeeding and childhood asthma-related symptoms. *Eur Respir J* 2012;39:81–9.
- 4 Ip S, Chung M, Raman G, *et al*. Breastfeeding and maternal and infant health outcomes in developed countries. *Evid Rep Technol Assess* 2007;153:1–186.
- 5 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.
- 6 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;360:901–7.
- 7 Grabenhenrich LB, Gough H, Reich A, *et al*. Early-life determinants of asthma from birth to age 20 years: a German birth cohort study. *J Allergy Clin Immunol* 2014;133:979–88.
- 8 Oren E, Rothers J, Stern DA, *et al*. Cough during infancy and subsequent childhood asthma. *Clin Exp Allergy* 2015;45:1439–46.
- 9 Taussig LM, Wright AL, Holberg CJ, *et al*. Tucson Children's Respiratory Study: 1980 to present. *J Allergy Clin Immunol* 2003;111:661–75.
- 10 Guilbert TW, Stern DA, Morgan WJ, *et al*. Effect of breastfeeding on lung function in childhood and modulation by maternal asthma and atopy. *Am J Respir Crit Care Med* 2007;176:843–8.
- 11 Sherrill DL, Guerra S, Minervini MC, *et al*. The relation of rhinitis to recurrent cough and wheezing: a longitudinal study. *Respir Med* 2005;99:1377–85.
- 12 Wright AL, Holberg CJ, Morgan WJ, *et al*. Recurrent cough in childhood and its relation to asthma. *Am J Respir Crit Care Med* 1996;153(4 Pt 1):1259–65.
- 13 Berry CE, Billheimer D, Jenkins IC, *et al*. A distinct low lung function trajectory from childhood to the fourth decade of life. *Am J Respir Crit Care Med* 2016;194:607–12.
- 14 Stein RT, Sherrill D, Morgan WJ, *et al*. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;354:541–5.
- 15 Lombardi E, Morgan WJ, Wright AL, *et al*. Cold air challenge at age 6 and subsequent incidence of asthma. A longitudinal study. *Am J Respir Crit Care Med* 1997;156:1863–9.
- 16 Martinez FD, Wright AL, Taussig LM, *et al*. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332:133–8.
- 17 Stern DA, Lohman IC, Wright AL, *et al*. Dynamic changes in sensitization to specific aeroallergens in children raised in a desert environment. *Clin Exp Allergy* 2004;34:1563–669.
- 18 Fredriksson P, Jaakkola N, Jaakkola JJ. Breastfeeding and childhood asthma: a six-year population-based cohort study. *BMC Pediatr* 2007;7:39.
- 19 Sucharew H, Ryan PH, Bernstein D, *et al*. Exposure to traffic exhaust and night cough during early childhood: the CCAAPS birth cohort. *Pediatr Allergy Immunol* 2010;21(2 Pt 1):253–9.
- 20 Wright AL, Holberg CJ, Taussig LM, *et al*. Relationship of infant feeding to recurrent wheezing at age 6 years. *Arch Pediatr Adolesc Med* 1995;149:758–63.
- 21 Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. *J Pediatr* 2001;139:261–6.
- 22 Wright AL, Sherrill D, Holberg CJ, *et al*. Breast-feeding, maternal IgE, and total serum IgE in childhood. *J Allergy Clin Immunol* 1999;104(3 Pt 1):589–94.
- 23 Wheaton AG, Ford ES, Thompson WW, *et al*. Pulmonary function, chronic respiratory symptoms, and health-related quality of life among adults in the United States--National Health and Nutrition Examination Survey 2007–2010. *BMC Public Health* 2013;13:854.
- 24 Bridevaux PO, Gerbase MW, Probst-Hensch NM, *et al*. Long-term decline in lung function, utilisation of care and quality of life in modified GOLD stage 1 COPD. *Thorax* 2008;63:768–74.
- 25 Cerveri I, Brusasco V. Revisited role for mucus hypersecretion in the pathogenesis of COPD. *Eur Respir Rev* 2010;19:109–12.
- 26 Blanc FX, Macedo P, Hew M, *et al*. Capsaicin cough sensitivity in smokers with and without airflow obstruction. *Respir Med* 2009;103:786–90.
- 27 Verduci E, Banderali G, Barberi S, *et al*. Epigenetic effects of human breast milk. *Nutrients* 2014;6:1711–24.

- 28 Celedón JC, Litonjua AA, Ryan L, *et al.* Bottle feeding in the bed or crib before sleep time and wheezing in early childhood. *Pediatrics* 2002;110:e77.
- 29 Soto-Ramírez N, Karmaus W, Zhang H, *et al.* Modes of infant feeding and the occurrence of coughing/wheezing in the first year of life. *J Hum Lact* 2013;29:71–80.
- 30 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;185:874–80.
- 31 Owens L, Laing IA, Zhang G, *et al.* Can risk factors for COPD be traced back to infancy? The Perth infant asthma follow up study. *European Respiratory Journal* 2016;48.
- 32 Khuc K, Blanco E, Burrows R, *et al.* Adolescent metabolic syndrome risk is increased with higher infancy weight gain and decreased with longer breast feeding. *Int J Pediatr* 2012;2012:1–6.
- 33 Rigas A, Rigas B, Glassman M, *et al.* Breast-feeding and maternal smoking in the etiology of Crohn's disease and ulcerative colitis in childhood. *Ann Epidemiol* 1993;3:387–92.
- 34 Oddy WH. Long-term health outcomes and mechanisms associated with breastfeeding. *Expert Rev Pharmacoecon Outcomes Res* 2002;2:161–77.
- 35 Buescher ES. Anti-inflammatory characteristics of human milk: how, where, why. *Adv Exp Med Biol* 2001;501:207–22.