

Breast feeding in infancy and recurrent cough in adulthood: the longer the better?

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Breast feeding has been associated with many beneficial outcomes in children. Among other benefits, it has been linked to lower infant mortality,¹ lower risk of sudden infant death syndrome,² lower incidence of certain types of cancer³ and even higher intelligence.⁴ In terms of atopy and respiratory diseases, it has been associated with decreased risk of lower respiratory infections (LRIs)⁵ and childhood asthma (particularly over the first few years of life).^{6,7} On the other hand, a recent meta-analysis found no strong evidence that breast feeding helps prevent food allergies, eczema or allergic rhinitis.⁸ However, many studies looking at respiratory outcomes recorded breast feeding retrospectively or failed to thoroughly control for potentially important confounders.⁹

Whether these benefits extend into adulthood is still an open question. For example, a history of breast feeding may not affect the risk of high total cholesterol, high blood pressure or cardiovascular mortality.¹⁰ Unfortunately, studies evaluating the association between breast feeding and asthma in adults are scarce and have provided somewhat concerning results. In the Dunedin cohort, Sears *et al* reported an ~83% increased risk of asthma at 9–26 years of age among participants who were breast fed in infancy compared with those who were not breast fed.¹¹ Likewise, the Tasmanian Asthma Study reported that exclusively breastfed children (of mothers with a history of atopy) had 46%–83% higher risk of asthma at 14, 32 and 44 years of age, with similar results for allergic rhinitis.¹² However, these cohorts were recruited at 3 and 7 years of age, respectively, and thus breastfeeding information may have been subject to recall bias.

In their study, Gerhart *et al*¹³ go a step further to answer the question of whether breast feeding is associated with respiratory symptoms later in life. Using data from the Tucson Children's Respiratory Study (TCRS)—perhaps the most

influential epidemiological birth cohort of childhood asthma—the authors evaluate the association between breastfeeding duration and the presence of recurrent cough in 735 cohort participants at 22, 26 and 32 years of age. They report that breast feeding for ≥ 4 months is associated with ~28% lower risk of recurrent cough during early adulthood (adjusted OR 0.72, 95% CI 0.56 to 0.90) after adjusting for sex, race/ethnicity and participant smoking, as well as parental age, education, smoking and asthma. The results are very interesting and point to very long-term effects of breast feeding on respiratory symptoms. Chief among the strengths of the study are the use of detailed data collected prospectively during infancy, the non-selected nature of the original cohort and the relatively high participation rate (~59% of the original sample) even three decades later. The study limitations are clearly disclosed by the authors and include the differences between mothers who breast fed and those who did not, the use of self-report to collect adult symptoms (including the outcome) and the fact that subjects who were breast fed for longer as infants were more likely to still be in the cohort at age 32 years.

Exactly *how* might longer breast feeding protect from recurrent cough 30 years later is not clear. Perhaps the simplest explanation would be that breast feeding is associated with lower risk of asthma, and thus with lower odds of cough; however, the authors report no association between breastfeeding duration and adult asthma, and that additional adjustment for asthma did not alter their results. As the authors suggest, another plausible explanation may include protection from early-life viral LRIs among infants who have been breast fed for a longer period of time which may in turn protect from respiratory symptoms later in life. In this study, early LRI-related wheezing and respiratory syncytial virus (RSV) infections were not associated with recurrent cough in adulthood, although there were some non-significant 'trends' (RSV LRI vs cough at 22 years, $p=0.07$; and childhood wheezing phenotype vs cough at 22–32 years, $p=0.06$). Thus, we may not be able

to completely rule out the potential mediating role of protection from viral LRIs or early wheeze. Another possibility would be that immune globulins or other factors in breast milk may modulate the microbiome^{14,15} or induce epigenetic changes¹⁶ during a time period that is crucial for the infant's immune system development and maturation. Infant feeding patterns have been associated with other diseases, such as Crohn's disease, ulcerative colitis¹⁷ or diabetes,¹⁸ in which immunity and inflammation also play prominent roles.

Of interest, in the study by Gerhart *et al* participants with earlier introduction of formula were more likely to report tobacco smoking at 22 years (but not at 26 or 32 years), and participant smoking was associated with recurrent cough (and with wheezing) at all three time points. Moreover, maternal and paternal smoking were associated with shorter breastfeeding duration. While the statistical models were adjusted for participant and parental smoking, these associations may reflect unmeasured or unknown factors that may partly affect the risk of recurrent cough. The same may be true for data completeness: participants who were breast fed longer were more likely to still be in the study at age 32. While this only happened at the last time point, that visit was precisely the one with the most statistically robust association, and this may suggest that there are some unmeasured characteristics of study participants that associate with breast feeding and that could partially explain the risk of recurrent cough. Other potential confounders include rhinitis, chronic sinusitis and heartburn, all of which were more frequently reported by subjects with recurrent cough. However, adjusting for these characteristics did not alter the results, making it less likely that these diseases were responsible for the observed associations.

Finally, another interesting possibility would be that lung function (or lung function deficits) might mediate the reported results. Given the association between breastfeeding duration and forced vital capacity (FVC) at 16 years of age in the TCRS cohort,¹⁹ the authors adjusted the models in the current study for FVC and found no significant changes in their results. However, they did not evaluate forced expiratory volume in 1s (FEV₁) or FEV₁/FVC. This is particularly important because breast feeding has been associated with higher FEV₅₀ in adolescents²⁰ and with higher FEV₁/FVC in young adults²¹ and, as the authors note, recurrent cough in older

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adults has been associated with airway obstruction.²² One could hypothesise that breast feeding may lead to improved lung function early on (or to reduced risk of airway obstruction) which is in turn reflected in a reduced risk of chronic cough later in life.

A thought-provoking question that arises but remains unanswered is whether results like these provide a glimpse of a link between protective (or risk) factors for childhood asthma and those for adult lung diseases such as chronic obstructive pulmonary disease (COPD). The 'Dutch hypothesis' was first proposed in 1961 to suggest that asthma and COPD had common origins, and their clinical expressions were part of a 'spectrum'.²³ Could it be that breast feeding is somehow a piece of the puzzle? More importantly, one of the main ideas formulated with the Dutch hypothesis was to not simply apply a disease label but to carefully characterise patients (what we now call 'phenotyping'), taking into account the interplay between host and environmental factors.²³ We are all certainly hopeful that the TCRS and other long-term birth or early-life cohorts will continue to follow their altruistic participants for many years to come, and will continue to shed light on the evolution of respiratory health and disease throughout the lifespan.

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