



Gastroesophageal reflux and asthma: when, how, and why

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Purpose of review

Gastro-esophageal reflux is a possible cause of uncontrolled symptoms of asthma and should be actively investigated and treated before severe asthma is diagnosed and biological therapy started.

Recent findings

Recent investigations on esophageal function and tissue biomarkers in patients with asthma and associated GERD have established a relevant role for esophageal motility and neuronal sensory abnormalities in linking the two diseases. Characterization of the underpinning inflammatory substrate has showed mixed results as both neutrophilic and eosinophilic type 2 inflammatory changes have been described.

Summary

New findings regarding inflammatory mechanisms in GERD-associated asthma as well as new diagnostic tools to investigate functional esophageal abnormalities and characterize asthma endotype have identified potential treatable traits that may improve the clinical management and outcome of asthmatic patients with GERD.

Keywords

asthma, cough, gastroesophageal reflux disease, obesity, obstructive sleep apnea

INTRODUCTION

Asthma is a common chronic inflammatory disease of the airways associated to airway hyperreactivity and reversible airflow obstruction. Several symptoms may overlap with other conditions, such as chronic obstructive pulmonary disease (COPD) and gastroesophageal reflux disease (GERD) [1]. A proportion of about 5–10% of patients need high-dose medical therapy to be kept under control or remain uncontrolled despite such a treatment: they are defined as ‘severe asthmatic patients’ [2]. However, several asthma comorbidities, including GERD, may impact on asthma increasing its severity or mimicking its symptoms [3].

GERD is defined according to the Montreal consensus conference, as ‘a condition, which develops when the reflux of gastric contents cause troublesome symptoms and/or complications’ [4]. The pathophysiology of the disease is multifactorial, with mechanical incompetence of the lower esophageal sphincter (LES) playing a prominent role. However, abnormalities in peristaltic activity, anatomical variations of the diaphragm, presence of hiatal hernia [5] as well as other factors that still have to be identified contribute to its pathophysiology [6]. Heartburn,

which characteristically arises in the epigastric and retrosternal areas and projects cranially to the throat and neck, is the main symptom. A constellation of other extra-esophageal, mainly respiratory symptoms (i.e. chronic cough and asthma-like symptoms), may, however, make the diagnosis elusive [6].

GASTROESOPHAGEAL REFLUX DISEASE AND ASTHMA: EPIDEMIOLOGICAL ASSOCIATION

Prevalence of both asthma and GERD are increasing in many countries (mainly northern and western countries), posing a great burden on healthcare systems in terms of direct and indirect costs [1,7]:

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KEY POINTS

- Asthma and GERD are frequently encountered together in clinical practice and may interact in a vicious cycle with each other and with other comorbidities.
- Before diagnosing severe asthma, GERD has to be actively investigated and treated by means of empirical trial or based on objective evidence of reflux.
- Given the multitude of pathways at play in connecting digestive and airway diseases, a treatable trait approach should be implemented in clinical management of patients with asthma and GERD.

prevalence of asthma is estimated about 10% of the population [8], whereas GERD affects up to 20–40% of general population [9].

As previously mentioned, GERD is often associated to asthma. Overall, GERD has an estimated prevalence in asthmatic patients ranging 30–90% [10–12].

On the other hand, data on the estimated prevalence of asthma in GERD patients is scarcer [13].

In addition to raw prevalence estimation data, GERD and asthma seem to be associated by more than simple chance, leading to the hypothesis that pathological connections between the diseases exist [9]. Longitudinal studies have in fact identified asthma as a risk factor for GERD [14,15] and vice versa [14].

ETIOPATHOLOGICAL MECHANISMS AND MULTIDIRECTIONAL INTERACTIONS

The causal association between asthma and GERD can be explained by the so-called '*reflux*' and '*reflex*' theories. The '*reflux theory*' posits that direct aspiration of gastric juices into the airways and lungs results in damage to the epithelium, cytokines release, and chronic inflammation leading to airway hyper-responsiveness and obstruction [16²²,17]. The macro-aspiration of gastric contents into the tracheobronchial tree can complicate to acute chemical pneumonitis or *ab-ingestis*, which often leads to secondary bacterial pneumonia and adult respiratory distress syndrome.

The '*reflex theory*' stands on the common embryological origin and vagal innervation of the bronchial tree and esophagus, the latter of which may lead to bronchoconstriction when stimulated by gastric content. Instillation of acid into the esophagus triggers vagal reflexes and neuro-inflammation, leading to increased upper airway reactivity [16²²]. The pH of the esophagus is imbalanced because of reflux of the gastric contents. As the esophagus and the bronchial

tree is innervated by the vagus nerve, the imbalance in pH causes the sensitive receptors in the distal esophagus gets stimulated, leading to bronchoconstriction as a vagal reflex [18]. Neuro-inflammation in airway hyper-responsiveness demonstrates reverberating circuits in the central nervous system, which increases the frequency of vagal efferent impulses, highlighting the function of the axon reflex in increasing the local neuro-inflammatory changes in the lung [19]. Asthma is known to aggravate the symptoms of GERD: it may cause lung hyperinflation, and subsequent descent of the esophagus in the area of the lung hyperinflation, which raises the pressure gradient between the abdomen and chest [20]. The change in pressure gradient is associated with increased work of breathing also known as dysfunctional breathing, which is evidenced by deep sighing, thoracic-dominant breathing, mouth breathing, accessory muscle use even at rest and thoraco-abdominal asynchrony [21]. Asthma causes negative intrathoracic pleural pressure, increasing the intensity of the diaphragmatic pressure, leading to regurgitation of gastric content through the lower esophageal sphincter because of its herniation into the chest, which impairs the function of the lower esophageal sphincter. The medications administered during asthma, such as bronchodilators also may cause relaxation of the lower esophageal sphincter, leading to reflux of the gastric contents. Thus, the physiology of asthma and GERD is a vicious circle as asthma may induce GERD symptoms and GERD further worsens the symptoms of asthma [18,22].

ASTHMA, GASTROESOPHAGEAL REFLUX DISEASE, OBESITY, AND SLEEP DISORDERS: THE VICIOUS 'SQUARE'

Various epidemiological studies have linked obesity as a risk factor for both GERD and asthma [23,24]. The risk of developing asthma in overweight and obese patients increases by 50% [25]: several explanations have been put forward to better describe this increased incidence, including direct mechanical effects of obesity on respiratory physiology, dietary and lifestyle factors, direct inflammatory effects of obesity on respiratory airways, and obesity-related sleep disorders [16²²]. The mechanisms responsible for increased risk of GERD in obese patients reside predominantly in physiological abnormalities [26]: in a study by Suter *et al.* of 25.6% of 345 bariatric patients showed abnormal findings at esophageal manometry [27]. Also, transient relaxations of the lower esophageal sphincter (TRLES) have been found to be more prevalent in the obese population, especially during the 2-h postprandial period.

About 74 to 90% of patients with asthma may experience worsening of symptoms during the night

[28,29] and serious life-threatening exacerbations may occur during this period in a range from 40 to 53% of cases [30–33]. This is secondary to functional changes that occur in ventilation during sleep, airway responsiveness, inflammation, mucociliary clearance, hormone levels and homeostatic and ventilatory responses to hypercapnia and hypoxia [34,35].

Obstructive sleep apnea (OSA), characterized by multiple episodes of airflow obstruction during sleep because of collapse of upper airway structure leading to sleep disruption, arousal, and poor sleep quality, is often associated with GERD and laryngopharyngeal reflux (LPR). This could depend on a vicious circle that is initially triggered by airway obstruction. As an airway obstruction develops, the progressive increase in respiratory effort to breathe produces greater intrathoracic negative pressure that could exceed the containment function of the lower esophageal sphincter, promoting reflux of gastric contents into the esophagus and upper airways, contributing to local inflammation and tissue damage of the upper airways [36–41]. The American Academy of Sleep Medicine reports that obesity is a major risk factor to develop OSA [42,43], and a 10% weight gain could increase by six-fold the odds of developing moderate-to-severe OSA [44,45]. OSA has been also suggested to be linked to the development and/or worsening of asthma by several mechanisms, mainly mediated by the interaction between OSA, GERD, obesity, and lower airway inflammation [46] (Fig. 1).

GASTROESOPHAGEAL REFLUX DISEASE AND ASTHMA: BURDEN ON QUALITY OF LIFE

In the last two decades, the assessment of Health-Related Quality of Life (HRQoL) allowed to detect

the impact of asthma on patient's experience [47]. In addition to being bothered by the presence of symptoms, patients report limitations in physical activity, work, sleep quality, and social life. Moreover, negative effects on emotions, mood, and psychological well being are common features.

Although asthma and GERD often coexist, there is little research currently being conducted to explore the added effect of comorbid GERD on HRQoL of patients with asthma.

Asthmatic patients with GERD had significantly more impaired HRQoL because of the associated cough compared with those without GERD; patients with both diseases have significant lower scores in physical, psychological, and social domains of Leicester Cough Questionnaire (LCQ) [48] even when asthma control is achieved [49]. More recently, two studies of Kanemitsu *et al.* [50,51] have shown that a lower cough-specific QoL was associated with more GERD symptoms. Even if silent, gastroesophageal reflux is associated with significantly worse asthma-related QoL as measured by the mini-Asthma Quality of Life Questionnaire (mini-AQLQ). Moreover, patients with evidence of proximal reflux, compared with those participants without proximal reflux, had poorer mini-AQLQ scores and significantly lower mean physical score on the The Short Form (36) Health Survey (SF-36), a generic health status measure [52].

In a sample of 164 older asthmatic patients, physician-diagnosed GERD was a predictor of poorer quality of life related to asthma [53].

Also, in a randomized double-blind placebo-controlled trial with lansoprazole 30 mg twice daily for 24 weeks, the minimal clinically important difference was achieved for Asthma Quality of Life Questionnaire (AQLQ) overall score, symptom, and emotional domains [54].

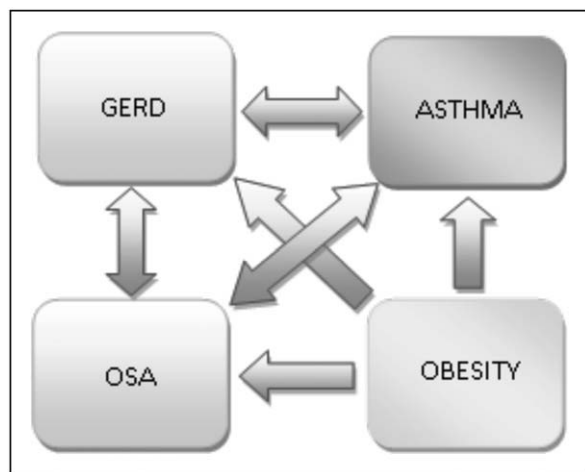


FIGURE 1. The vicious 'square' among asthma, gastroesophageal reflux disease, obesity and sleep disorders.

COUGH IN ASTHMATIC PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE: CONFOUNDING FACTOR OR SYMPTOM OF ASTHMA?

A frequent expression of extra-esophageal GERD is the cough-reflux syndrome, which has been matter of intensive investigation and has been regularly addressed by guidelines and position papers across the last two decades [55–57].

Cough in GERD may represent the only clinical-presenting symptom [58] or be part of a set of symptoms, such as hoarseness, dysphonia, globe sensation, and dysphagia, arising from the involvement of the upper airways. An ongoing line of investigation has identified gastroesophageal dysmotility in GERD-associated cough as a potential treatable trait [59–61]. In a

recent study, Li *et al.* in 2019 used ambulatory combined pH-impedance-pressure monitoring and demonstrated that both patients with GERD and chronic cough had low pan-esophageal pressure in primary peristalsis and synchronous contraction in secondary peristalsis [62[°]]. The clinical evidence that cough may be the only or predominant clinical expression of either GERD [58] or asthma, namely cough-variant asthma (CVA) and cough-predominant asthma, raises thus the need for diagnostic tools to segregate the two conditions. Actually, some markers might help identify GERD-induced cough, and thus inform therapeutic efforts in chronic cough patients with or without concomitant asthma. First, even though past evidence seemed not to support the idea that clinical features of cough could be specific for discrete diagnoses [63], new evidence seems to suggest the opposite [64,65^{°°}]. In particular, being physiologically linked to TRLES, reflux-cough is typically triggered by lying down, rising, eating, and phonating [65^{°°},66]. Hoarseness and throat clearing are usually associated symptoms but rather nonspecific. Heartburn and regurgitation are highly suggestive of reflux-cough but their absence does not rule out cough associated with nonacidic reflux events. On the other hand, nocturnal cough alone is highly suggestive for CVA and postnasal dripping indicates upper airway cough syndrome with high specificity [65^{°°}].

A number of questionnaires have been developed and validated in an attempt to define the severity of cough and to identify subgroups of patients with a high pretest probability of a specific disease, thus predicting effectiveness of targeted therapeutic trials. Reflux symptom index (RSI) scoring and Gastroesophageal reflux disease Questionnaire (GerdQ) can be used to identify LPR and GERD respectively, even though low specificity and inconsistent cut-off scores are main limitations [67]. The GerdQ is used for predicting acid GERD but is inferior to multichannel intraluminal impedance and pH monitoring (MII-pH) in detecting nonacid GERD [68].

Physical examination may help identify inflammatory changes associated with reflux-cough. MII-pH analysis confirmed GERD diagnosis in less than 40% of patients with previous diagnosis of LPR, most likely because of the low specificity of the laryngoscopy findings [69].

As to biomarkers of airway inflammation, a number of molecules and cells from different bio-sources have been investigated: [70]:

- (1) Tachykinins, marker of neurogenic inflammation, was found increased in sputum of asthmatic patients with GERD-related cough compared with non-GERD asthmatic patients [71].

- (2) Lipid-laden macrophage and bile salts in broncho-alveolar lavage (BAL) [72] seem to represent valuable markers of micro-aspiration but the invasiveness of the procedure makes it not applicable in daily clinical practice [70].
- (3) Decrease in exhaled breath condensate pH and increase in cysteinyl-leukotriens have been proposed as specific markers to identify a subgroup of patients with acidic GERD responsive to leukotriene receptor antagonism [73].

Recently, Wang *et al.* [74] proposed salivary pepsin as a valuable marker for the diagnosis of GERD and GERD-related disorders, especially when complemented by 24-h esophageal pH monitoring.

Exhaled nitric oxide (FENO) is a noninvasive biomarker of type 2 airway inflammation [75], and it has been investigated for its usefulness in discriminating CVA from GERD-cough or characterizing residual cough in otherwise well controlled asthma: low FENO levels would make CVA unlikely [76–80]. Notwithstanding intriguing progress in the field, no biomarker has hitherto gained an established and nonarbitrary role in the diagnostic work-up of chronic cough [70].

The broad differential diagnosis of chronic cough, the presumed lack of specificity for discrete diseases and the invasiveness of most diagnostic tools has fostered the use of therapeutic trials as diagnostic criteria. Anyway, when clinical assessment is noncontributory or first-line empiric treatment fails, objective evidence of reflux and as well as its temporal correlation to cough [81] should be obtained by using 24-h intra-esophageal pH monitoring, impedance monitoring [82], and cough-recording devices [83]. Twenty-four-hour pH-impedance pressure monitoring allows for identification of reflux episodes of different degrees of acidity and correlations with bursts of cough and disorders of esophageal motility. This has been shown to be of importance in subgroups of patients with chronic unexplained cough [84] or with disorders of esophageal motility, informing treatment decisions, such as the use of neuromodulators or pro-kinetics [85].

According to local experience and availability of diagnostic tests, work-up of chronic cough usually include sequences of therapeutic trials driven by symptom scores and objective evidence of functional abnormalities. We believe that if CVA and cough-reflux symptoms are primarily suspected, objective noninvasive diagnostic tests, such as FENO and bronchial challenge, should be preferred to empiric treatment during the early stages of the diagnostic work-up. CHS should be actively investigated at every step of the work-up with targeted clinical questionnaires

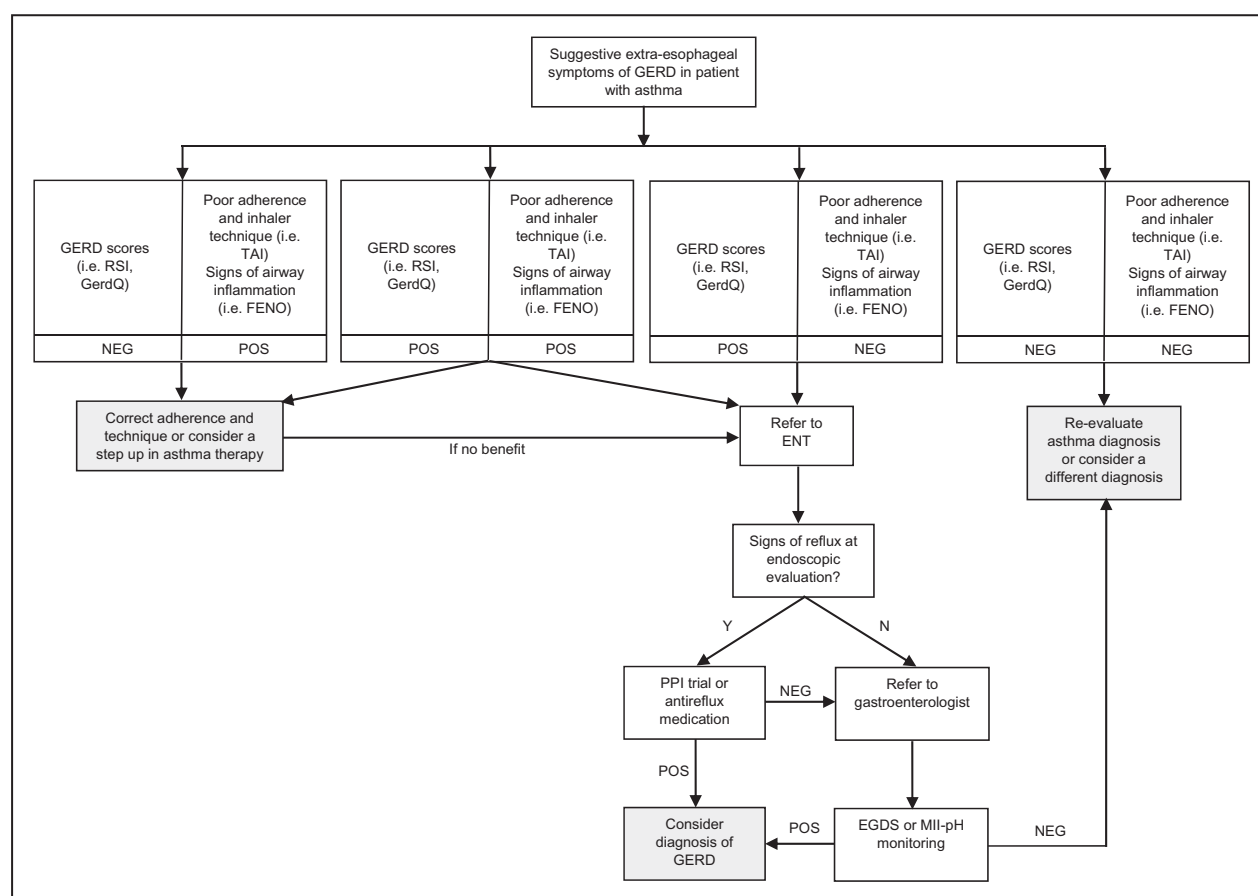


FIGURE 2. Proposed diagnostic algorithm for extra-esophageal symptoms of gastroesophageal reflux disease in patient with asthma.

and confirmed by trained laryngologists [86]. If CHS is confirmed, gabapentin and amitriptyline are potential therapeutic options in addition to controlling underlying diseases (Fig. 2).

HOW TO MANAGE ASSOCIATED GASTROESOPHAGEAL REFLUX DISEASE AND ASTHMA

Treatment with lifestyle changes, such as weight loss and elevation of the head of the bed [87], and daily proton pump inhibitors (PPIs) can be initiated [88], although PPI use is generally disappointing in improving respiratory symptoms. In the past years, several randomized control trials examined the effects of GERD treatment on asthma [10,12,89–93] but a significant and curative treatment was not identified [94]. From 2005, several trials have been conducted to investigate the effects of PPIs on asthma in GERD patients [54,95–97]. The treatment with PPIs has shown variable effects on asthma outcomes, mostly on quality of life and nocturnal symptoms but its effect on lung function and exacerbation seems to be controversial [98]. Although the current guidelines do not recommend

surgery for GERD that do not respond to PPI [99], several uncontrolled case series and a systematic review of antireflux surgery in asthma found that surgery may improve asthma symptoms control but no functional improvement [100–103]. Prokinetic agents are another feasible treatment for refractory GERD but to date there is no evidence to support this practice [104].

CONCLUSION

GERD can mimic asthma symptoms, such as cough variant asthma, or contribute to push asthma out of control through different and not fully identified inflammatory and neurogenic mechanisms. Whenever GERD is suspected because of suggestive symptoms and signs, diagnosis should be confirmed by means of therapeutic trials or objective evidence of pathological reflux (Fig. 2). Due to differences in local epidemiology, resources and research attitudes, widely variable diagnostic algorithms have been proposed in medical literature. We would like to suggest that noninvasive diagnostic tools, such as FENO, should be incorporated in the earliest stages of the work-up of GERD-associated asthma.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Global initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2020. Available at: www.ginasthma.org. [Accessed 16th September 2020].
2. Chung KF, Wenzel SE, Brozek JL, *et al.* International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43:343–373.
3. Porsbjerg C, Menzies-Gow A. Co-morbidities in severe asthma: clinical impact and management. *Respirology* 2017; 22:651–661.
4. Vakil N, van Zanten SV, Kahrilas P, *et al.* Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006; 101:1900–1920.
5. Patti MG. An evidence-based approach to the treatment of gastroesophageal reflux disease. *JAMA Surg* 2016; 151:73–78.
6. Cappell MS. Clinical presentation, diagnosis, and management of gastroesophageal reflux disease. *Med Clin North Am* 2005; 89:243–291.
7. World Gastroenterology Organisation Global Guidelines GERD Global Perspective on Gastroesophageal Reflux Disease Update October 2015. Available at: <https://www.worldgastroenterology.org/UserFiles/file/guidelines/gastroesophageal-reflux-disease-english-2015.pdf>. [Accessed 16 September 2020].
8. De Marco R, Cappa V, Accordini S, *et al.* Trends in the prevalence of asthma and allergic rhinitis in Italy between 1991 and. *Eur Respir J* 2012; 39:883–892.
9. Broers C, Tack J, Pauwels A. Review article: gastro-oesophageal reflux disease in asthma and chronic obstructive pulmonary disease. *Aliment Pharmacol Ther* 2018; 47:176–191.
10. Kiljander TO, Salomaa ER, Hietanen EK, Terho EO. Gastroesophageal reflux in asthmatics: a double-blind, placebo-controlled crossover study with omeprazole. *Chest* 1999; 116:1257–1264.
11. Harding SM. Acid reflux and asthma. *Curr Opin Pulm Med* 2003; 9:42–45.
12. Harding SM, Richter JE, Guzzo MR, *et al.* Asthma and gastroesophageal reflux: acid suppressive therapy improves asthma outcome. *Am J Med* 1996; 100:395–405.
13. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastroesophageal reflux disease: a systematic review. *Gut* 2005; 54:710–717.

14. Kim SY, Min C, Oh DJ, Choi HG. Bidirectional association between GERD and asthma: two longitudinal follow-up studies using a National Sample Cohort. *J Allergy Clin Immunol Pract* 2020; 8:1005e9–1013e9.
15. Ruigómez A, Rodríguez LA, Wallander MA, Johansson S, *et al.* Gastroesophageal reflux disease and asthma: a longitudinal study in UK general practice. *Chest* 2005; 128:85–93.
16. Gupta S, Lodha R, Kabra SK. Asthma, GERD and obesity: triangle of ■ inflammation. *Indian J Pediatr* 2018; 85:887–892.
17. This review article comprehensively describes the complex pathogenetic links between asthma, GERD, and obesity, suggesting a vicious cycle of interactions.
18. Gaude GS. Pulmonary manifestations of gastroesophageal reflux disease. *Ann Thorac Med* 2009; 4:115–123.
19. McCallister JW, Parsons JP, Mastronarde JG. The relationship between gastroesophageal reflux and asthma: an update. *Ther Adv Respir Dis* 2011; 5:143–150.
20. Stein MR. Possible mechanisms of influence of esophageal acid on airway hyperresponsiveness. *Am J Med* 2003; 115 Suppl 3A:55S–59S.
21. Ates F, Vaezi MF. Insight into the relationship between gastroesophageal reflux disease and asthma. *Gastroenterol Hepatol (N Y)* 2014; 10:729–736.
22. Denton E, Bondarenko J, Tay T, *et al.* Factors associated with dysfunctional breathing in patients with difficult to treat asthma. *J Allergy Clin Immunol Pract* 2019; 7:1471–1476.
23. Parsons JP, Mastronarde JG. Gastroesophageal reflux disease and asthma. *Curr Opin Pulm Med* 2010; 16:60–63.
24. Novosad S, Khan S, Wolfe B, Khan A. Role of obesity in asthma control, the obesity-asthma phenotype. *J Allergy (Cairo)* 2013; 2013:538642.
25. Raj D, Kabra SK, Lodha R. Childhood obesity and risk of allergy or asthma. *Immunol Allergy Clin North Am* 2014; 34:753–765.
26. Gibson PG. Obesity and asthma. *Ann Am Thorac Soc* 2013; 10 Suppl:S138–S142.
27. Chang P, Friedenberg F. Obesity and GERD. *Gastroenterol Clin North Am* 2014; 43:161–173.
28. Stein DJ, El-Serag HB, Kuczynski J, *et al.* The association of body mass index with Barrett's oesophagus. *Aliment Pharmacol Ther* 2005; 22:1005–1010.
29. Turner-Warwick M. Epidemiology of nocturnal asthma. *Am J Med* 1988; 85(1B):6–8.
30. Douglas NJ, Flenley DC. Breathing during sleep in patients with obstructive lung disease. *Am Rev Respir Dis* 1990; 141(4 Pt 1):1055–1070.
31. Horn CR, Clark TJ, Cochrane GM. Is there a circadian variation in respiratory morbidity? *Br J Dis Chest* 1987; 81:248–251.
32. Douglas NJ. Asthma at night. *Clin Chest Med* 1985; 6:663–674.
33. Douglas NJ. Nocturnal asthma. *Q J Med* 1989; 71:279–289.
34. Robertson CF, Rubinfeld AR, Bowes G. Deaths from asthma in Victoria: a 12-month survey. *Med J Aust* 1990; 152:511–517.
35. Khan WH, Mohsenin V, D'Ambrosio CM. Sleep in asthma. *Clin Chest Med* 2014; 35:483–493.
36. Kavanagh J, Jackson DJ, Kent BD. Sleep and asthma. *Curr Opin Pulm Med* 2018; 24:569–573.
37. Altıntaş A, Soylu A, Yegin Y, *et al.* Impact of laryngopharyngeal reflux on the levels of depression and anxiety in patients with obstructive sleep apnea syndrome. *J Craniofac Surg* 2017; 28:e121–e124.
38. Elhennawi DM, Ahmed MR, Abou-Halawa AS. Correlation of obstructive sleep apnoea and laryngopharyngeal reflux: phmetry study. *Clin Otolaryngol* 2016; 41:758–761.
39. Qu Y, Ye JY, Han DM, *et al.* Esophageal functional changes in obstructive sleep apnea/hypopnea syndrome and their impact on laryngopharyngeal reflux disease. *Chin Med J (Engl)* 2015; 128:2162–2167.
40. Rodrigues MM, Dibbern RS, Santos VJ, Passeri LA. Influence of obesity on the correlation between laryngopharyngeal reflux and obstructive sleep apnea. *Braz J Otorhinolaryngol* 2014; 80:5–10. (in English, Portuguese).
41. Xavier SD, Moraes JP, Eckley CA. Prevalence of signs and symptoms of laryngopharyngeal reflux in snorers with suspected obstructive sleep apnea. *Braz J Otorhinolaryngol* 2013; 79:589–593. (in English, Portuguese).
42. Laohasiriwong S, Johnston N, Woodson BT. Extra-esophageal reflux, NOSE score, and sleep quality in an adult clinic population. *Laryngoscope* 2013; 123:3233–3238.
43. Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. *JAMA* 2004; 291:2013–2016.
44. Schwartz AR, Patil SP, Laffan AM, *et al.* Obesity and obstructive sleep apnea: pathogenic mechanisms and therapeutic approaches. *Proc Am Thorac Soc* 2008; 5:185–192.
45. Peppard PE, Young T, Barnet JH, *et al.* Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013; 177:1006–1014.
46. Pillar G, Shehadeh N. Abdominal fat and sleep apnea: the chicken or the egg? *Diabetes Care* 2008; 31 Suppl 2:S303–S309.
47. Salles C, Terse-Ramos R, Souza-Machado A, Cruz AA. Obstructive sleep apnea and asthma. *J Bras Pneumol* 2013; 39:604–612.
48. Wilson SR, Rand CS, Cabana MD, *et al.* Asthma outcomes: quality of life. *J Allergy Clin Immunol* 2012; 129(3 Suppl):S88–123.
49. Shirai T, Mikamo M, Tsuchiya T, *et al.* Real-world effect of gastroesophageal reflux disease on cough-related quality of life and disease status in asthma and COPD. *Allergol Int* 2015; 64:79–83.

49. Shirai T, Mikamo M, Shishido Y, *et al*. Impaired cough-related quality of life in patients with controlled asthma with gastroesophageal reflux disease. *Ann Allergy Asthma Immunol* 2012; 108:379–380.
 50. Kanemitsu Y, Niimi A, Matsumoto H, *et al*. Gastroesophageal dysmotility is associated with the impairment of cough-specific quality of life in patients with cough variant asthma. *Allergol Int* 2016; 65:320–326.
 51. Kanemitsu Y, Kurokawa R, Takeda N, *et al*. Clinical impact of gastroesophageal reflux disease in patients with subacute/chronic cough. *Allergol Int* 2019; 68:478–485.
 52. DiMango E, Holbrook JT, Simpson E, *et al*. American Lung Association Asthma Clinical Research Centers. Effects of asymptomatic proximal and distal gastroesophageal reflux on asthma severity. *Am J Respir Crit Care Med* 2009; 180:809–816.
 53. Kannan JA, Bernstein DI, Bernstein CK, *et al*. Significant predictors of poor quality of life in older asthmatics. *Ann Allergy Asthma Immunol* 2015; 115:198–204.
 54. Littner MR, Leung FW, Ballard ED 2nd, *et al*. Lansoprazole Asthma Study Group. Effects of 24 weeks of lansoprazole therapy on asthma symptoms, exacerbations, quality of life, and pulmonary function in adult asthmatic patients with acid reflux symptoms. *Chest* 2005; 128:1128–1135.
 55. Irwin RS. Chronic cough due to gastroesophageal reflux disease: ACCP evidence-based clinical practice guidelines. *Chest* 2006; 129(1 Suppl):80S–94S.
 56. Kahrlas PJ, Altman KW, Chang AB, *et al*. CHEST Expert Cough Panel. Chronic cough due to gastroesophageal reflux in adults: CHEST Guideline and Expert Panel Report. *Chest* 2016; 150:1341–1360.
 57. Irwin RS, French CL, Chang AB, *et al*. CHEST Expert Cough Panel. Classification of cough as a symptom in adults and management algorithms: CHEST Guideline and Expert Panel Report. *Chest* 2018; 153:196–209.
 58. Irwin RS, Zawacki JK, Curley FJ, *et al*. Chronic cough as the sole presenting manifestation of gastroesophageal reflux. *Am Rev Respir Dis* 1989; 140:1294–1300.
 59. Knight RE, Wells JR, Parrish RS. Esophageal dysmotility as an important cofactor in extraesophageal manifestations of gastroesophageal reflux. *Laryngoscope* 2000; 110:1462–1466.
 60. Lin S, Li H, Fang X. Esophageal motor dysfunctions in gastroesophageal reflux disease and therapeutic perspectives. *J Neurogastroenterol Motil* 2019; 25:499–507.
 61. Jiang L, Ye B, Wang Y, *et al*. Esophageal body motility for clinical assessment in patients with refractory gastroesophageal reflux symptoms. *J Neurogastroenterol Motil* 2017; 23:64–71.
 62. Li X, Lin S, Wang Z, *et al*. Gastroesophageal reflux disease and chronic cough: a possible mechanism elucidated by ambulatory pH-impedance-pressure monitoring. *Neurogastroenterol Motil* 2019; 31:e13707.
- This study demonstrated that low pan-esophageal pressure in primary peristalsis and synchronous contraction in secondary peristalsis are present in both GERD and chronic cough patients.
63. Mello CJ, Irwin RS, Curley FJ. Predictive values of the character, timing, and complications of chronic cough in diagnosing its cause. *Arch Intern Med* 1996; 156:997–1003.
 64. Otoshi T, Nagano T, Funada Y, *et al*. A cross-sectional survey of the clinical manifestations and underlying illness of cough. *In Vivo* 2019; 33:543–549.
 65. Lai K, Zhan W, Li H, *et al*. The predicative clinical features associated with chronic cough that has a single underlying cause. *J Allergy Clin Immunol Pract* 2020; S2213-2198(20)30713-3. doi: 10.1016/j.jaip.2020.06.066. [Epub ahead of print]
- This recent article highlighted that specific symptoms can be identified in order to elucidate the causative role of GERD in chronic cough.
66. Everett CF, Morice AH. Clinical history in gastroesophageal cough. *Respir Med* 2007; 101:345–348.
 67. Barry DW, Vaezi MF. Laryngopharyngeal reflux: more questions than answers. *Cleve Clin J Med* 2010; 77:327–334.
 68. Xu X, Chen Q, Liang S, *et al*. Comparison of gastroesophageal reflux disease questionnaire and multichannel intraluminal impedance pH monitoring in identifying patients with chronic cough responsive to antireflux therapy. *Chest* 2014; 145:1264–1270.
 69. De Bortoli N, Nacci A, Savarino E, *et al*. How many cases of laryngopharyngeal reflux suspected by laryngoscopy are gastroesophageal reflux disease-related? *World J Gastroenterol* 2012; 18:4363–4370.
 70. Emilsson OL, Gislason T, Olin AC, Janson C, *et al*. Biomarkers for gastroesophageal reflux in respiratory diseases. *Gastroenterol Res Pract* 2013; 2013:148086.
 71. Patterson RN, Johnston BT, Ardill JE, *et al*. Increased tachykinin levels in induced sputum from asthmatic and cough patients with acid reflux. *Thorax* 2007; 62:491–495.
 72. Knauer-Fischer S, Ratjen F. Lipid-laden macrophages in bronchoalveolar lavage fluid as a marker for pulmonary aspiration. *Pediatr Pulmonol* 1999; 27:419–422.
 73. Heffler E, Crimi C, Brussino L, *et al*. Exhaled breath condensate pH and cysteinyl leukotriens in patients with chronic cough secondary to acid gastroesophageal reflux. *J Breath Res* 2016; 11:016002.
 74. Wang YJ, Lang XQ, Wu D, *et al*. Salivary pepsin as an intrinsic marker for diagnosis of sub-types of gastroesophageal reflux disease and gastroesophageal reflux disease-related disorders. *J Neurogastroenterol Motil* 2020; 26:74–84.
 75. Heffler E, Carpagnano GE, Favero E, *et al*. Fractional Exhaled Nitric Oxide (FENO) in the management of asthma: a position paper of the Italian Respiratory Society (SIP/IRS) and Italian Society of Allergy, Asthma and Clinical Immunology (SIAAIC). *Multidiscip Respir Med* 2020; 15:36.
 76. Feng-Jia C, Xin-Yan H, Geng-Peng L, *et al*. Validity of fractional exhaled nitric oxide and small airway function indices in diagnosis of cough-variant asthma. *J Asthma* 2018; 55:750–755.
 77. Song WJ, Kim HJ, Shim JS, *et al*. Diagnostic accuracy of fractional exhaled nitric oxide measurement in predicting cough-variant asthma and eosinophilic bronchitis in adults with chronic cough: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2017; 140:701–709.
 78. Zhang L, Liu S, Li M, Xu X. Diagnostic value of fractional exhaled nitric oxide in cough-variant asthma: an updated meta-analysis. *J Asthma* 2020; 57:335–342.
 79. Pizzimenti S, Heffler E, Piccioni P, *et al*. Usefulness of exhaled nitric oxide (FeNO) measured by a portable analyzer to diagnose cough variant asthma in a clinical setting of chronic cough. *Allergy* 2009; 64(S90):395.
 80. Asano T, Takemura M, Fukumitsu K, *et al*. Diagnostic utility of fractional exhaled nitric oxide in prolonged and chronic cough according to atopic status. *Allergol Int* 2017; 66:344–350.
 81. Weusten BL, Roelofs JM, Akkermans LM, *et al*. The symptom-association probability: an improved method for symptom analysis of 24-h esophageal pH data. *Gastroenterology* 1994; 107:1741–1745.
 82. Herregods TVK, Pauwels A, Jafari J, *et al*. Determinants of reflux-induced chronic cough. *Gut* 2017; 66:2057–2062.
 83. Houghton LA, Smith JA. Breaking the sound barrier? Pitfalls and benefits of acoustic cough monitoring. *Am J Gastroenterol* 2012; 107:1833–1836.
 84. Sifrim D, Dupont L, Blondeau K, *et al*. Weakly acidic reflux in patients with chronic unexplained cough during 24 h pressure, pH, and impedance monitoring. *Gut* 2005; 54:449–454.
 85. Yu Y, Wen S, Wang S, *et al*. Reflux characteristics in patients with gastroesophageal reflux-related chronic cough complicated by laryngopharyngeal reflux. *Ann Transl Med* 2019; 7:529.
 86. Lee JW, Tay TR, Paddle P, *et al*. Diagnosis of concomitant inducible laryngeal obstruction and asthma. *Clin Exp Allergy* 2018; 48:1622–1630.
 87. Kaltenbach T, Crockett S, Gerson LB. Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. *Arch Intern Med* 2006; 166:965–971.
 88. Smith JA, Woodcock A. Chronic cough. *N Engl J Med* 2016; 375:1544–1551.
 89. Boeree MJ, Peters FT, Postma DS, Kleibeuker JH. No effects of high-dose omeprazole in patients with severe airway hyperresponsiveness and (a)symptomatic gastro-oesophageal reflux. *Eur Respir J* 1998; 11:1070–1074.
 90. Ford RM. Asthma in Australia. *Aust N Z J Med* 1994; 24:71.
 91. Levin TR, Sperling RM, McQuaid KR. Omeprazole improves peak expiratory flow rate and quality of life in asthmatics with gastroesophageal reflux. *Am J Gastroenterol* 1998; 93:1060–1063.
 92. Meier JH, McNally PR, Punja M, *et al*. Does omeprazole (Prilosec) improve respiratory function in asthmatics with gastroesophageal reflux? A double-blind, placebo-controlled crossover study. *Dig Dis Sci* 1994; 39:2127–2133.
 93. Teichtahl H, Kronborg JJ, Yeomans ND, Robinson P. Adult asthma and gastro-oesophageal reflux: the effects of omeprazole therapy on asthma. *Aust N Z J Med* 1996; 26:671–676.
 94. Gibson PG, Henry RL, Coughlan JL. Gastro-oesophageal reflux treatment for asthma in adults and children. *Cochrane Database Syst Rev* 2003; (2):CD001496.
 95. Kiljander TO, Harding SM, Field SK, *et al*. Effects of esomeprazole 40 mg twice daily on asthma: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2006; 173:1091–1097.
 96. Writing Committee for the American Lung Association Asthma Clinical Research Centers. Holbrook JT, Wise RA, *et al*. Lansoprazole for children with poorly controlled asthma: a randomized controlled trial. *JAMA* 2012; 307:373–381.
 97. Kiljander TO, Junghard O, Beckman O, Lind T. Effect of esomeprazole 40 mg once or twice daily on asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med* 2010; 181:1042–1048.
 98. Chan WW, Chiou E, Obstein KL, *et al*. The efficacy of proton pump inhibitors for the treatment of asthma in adults: a meta-analysis. *Arch Intern Med* 2011; 171:620–629.
 99. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013; 108:308–328.
 100. Rothenberg S, Cowles R. The effects of laparoscopic Nissen fundoplication on patients with severe gastroesophageal reflux disease and steroid-dependent asthma. *J Pediatr Surg* 2012; 47:1101–1104.
 101. Field SK, Gelfand GA, McFadden SD. The effects of antireflux surgery on asthmatics with gastroesophageal reflux. *Chest* 1999; 116:766–774.
 102. Sontag SJ, O'Connell S, Khandelwal S, *et al*. Asthmatics with gastroesophageal reflux: long term results of a randomized trial of medical and surgical antireflux therapies. *Am J Gastroenterol* 2003; 98:987–999.
 103. Kiljander T, Rantanen T, Kellokumpu I, *et al*. Comparison of the effects of esomeprazole and fundoplication on airway responsiveness in patients with gastro-oesophageal reflux disease. *Clin Respir J* 2013; 7:281–287.
 104. Glicksman JT, Mick PT, Fung K, Carroll TL. Prokinetic agents and laryngopharyngeal reflux disease: prokinetic agents and laryngopharyngeal reflux disease: a systematic review. *Laryngoscope* 2014; 124:2375–2379.