Systematic review: the extra-oesophageal symptoms of gastro-oesophageal reflux disease in children

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SUMMARY
Background
Extra-oesophageal symptoms are thought to be common, atypical symptoms of gastro-oesophageal reflux disease (GERD) in children.

Aim
To investigate the prevalence of GERD in children with extra-oesophageal symptoms or of extra-oesophageal symptoms in children with GERD, and the effect of GERD therapies on extra-oesophageal symptoms.

Methods
A systematic review of articles in PubMed and EMBASE.

Results
We identified 18 relevant articles. The pooled weighted average prevalence of GERD in asthmatic children was 23%, compared with 4% in healthy controls from the same five studies. The majority of studies evaluating the relationship between apparent life-threatening event (ALTE) and GERD did not suggest a causal relationship. Seven studies reported that respiratory symptoms, sinusitis and dental erosion were significantly more prevalent in children with GERD than in controls. Data from pharmacotherapeutic trials were inconclusive and provided no support for a causal relationship between GERD and extra-oesophageal symptoms.

Conclusions
Possible associations exist between GERD and asthma, pneumonia, bronchiectasis, ALTE, laryngotracheitis, sinusitis and dental erosion, but causality or temporal association were not established. Moreover, the paucity of studies, small sample sizes and varying disease definitions did not allow firm conclusions to be drawn. Most trials of GERD therapies showed no improvement in extra-oesophageal symptoms in children.

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INTRODUCTION

Gastro-oesophageal reflux disease (GERD) in adults develops when reflux of the stomach contents into the oesophagus causes troublesome symptoms such as heartburn or acid regurgitation, and/or complications such as oesophagitis. However, there are less recognizable, extra-oesophageal symptoms of GERD, which affect various tissues and organ systems beyond the oesophagus. The recent Montreal Definition of GERD described established associations, although not necessarily causal, between adult GERD and cough, laryngitis, asthma and dental erosion. Associations with pharyngitis, sinusitis, idiopathic pulmonary fibrosis and recurrent otitis media have also been proposed in adults, but more data are needed to confirm a link with GERD.

Extra-oesophageal symptoms occur in a third of adult patients with GERD, whether or not reflux oesophagitis is present. Three large studies have shown that patients with GERD and individuals with GERD in the general population are up to three times more likely to have laryngeal or pulmonary conditions than those without GERD. Extra-oesophageal symptoms such as these are hypothesized to be caused by refluxate from the stomach reaching the respiratory tract or via stimulation of the oesophagobronchial reflex. It is also possible that symptoms such as cough and wheezing may cause reflux through an increase in intra-abdominal pressure.

A recent systematic review reported a significant association between GERD and asthma in adults, although a temporal sequence could not be determined. Fewer prevalence studies have been performed in the paediatric population. Only one systematic review of the association between extra-oesophageal symptoms and GERD in children has been published and this looked only at upper airway symptoms.

This systematic review aims to evaluate the presence and magnitude of the association between GERD in children and a range of extra-oesophageal symptoms, including those highlighted in the Montreal Definition, the systematic review by Rosbe et al. and the recently published Paediatric Definition of GERD, by assessing articles reporting the prevalence of GERD in children with extra-oesophageal symptoms or of extra-oesophageal symptoms in children with GERD, and studies assessing the effect of GERD therapies on extra-oesophageal symptoms.

METHODS

Search strategy and study selection

Studies were identified via systematic searches of PubMed and EMBASE using the search terms detailed in Figure 1. Searches were limited to journal articles reporting studies in humans aged 0–18 years.

Figure 1. Flow diagram showing selection of articles.
Editorials, letters, practice guidelines, reviews, case reports, comments and in vitro articles were excluded. Relevant studies presented at the World Congress of Paediatric Gastroenterology, Hepatology and Nutrition (WCPGHAN), United European Gastroenterology Week (UEGW), North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), and Digestive Disease Week (DDW) within the past 4 years were also identified from abstract titles.

Relevant studies were selected first on the basis of the title and then on the abstract, as outlined in Figure 1. Articles were then screened based on the full text; those that explored the association of GERD and extra-oesophageal symptoms in children and infants and those that studied the effect of anti-reflux medications on extra-oesophageal symptoms were selected. Studies presented at congresses were selected on the basis of the abstract text if enough information was included. Studies that did not have a control population and those not published in English were excluded.

The extra-oesophageal symptoms evaluated by our review process comprised: (i) respiratory conditions or symptoms: asthma, wheezing, cough, apnoea, bronchiitis, pneumonia, bronchiectasis and apparent life-threatening events (ALTE); (ii) conditions affecting the ear, nose and throat (ENT), such as sinusitis, otitis media and laryngotracheitis; (iii) dental erosion.

Tabulation of results and analysis

The full papers (or abstracts only for the articles from congresses) from the studies selected based on the content of their abstracts were analysed. For the studies exploring the association of gastro-oesophageal reflux and extra-oesophageal symptoms in children, the following data were collected: sample size, study design, method of data collection, definition of reflux symptoms, definition of extra-oesophageal symptoms and the reported prevalence estimate. Where enough data were available, we determined overall prevalence estimates by pooling values from studies meeting the selection criteria and calculating average values weighted by sample size. For the studies evaluating the impact of GERD therapies on extra-oesophageal symptoms, the following data were collected: sample size, study design, definition of reflux symptoms, definition of extra-oesophageal symptoms, drug administered, dosage and length of treatment period, and the study outcome.

RESULTS

The PubMed and EMBASE searches identified 903 articles, and a further 25 potential abstracts were selected from recent conferences. Of these, 241 relevant articles were selected. Those studies with no control population and those not published in English were then excluded, resulting in 18 that were evaluated in our review. The majority of articles were excluded because of the lack of a healthy control population.

Prevalence of extra-oesophageal symptoms and GERD in children

We identified 15 studies satisfying our criteria that reported the prevalence of GERD and extra-oesophageal symptoms in children (Tables 1 and 2). Of these, six examined the prevalence of extra-oesophageal symptoms in children with GERD (Figure 2), while nine focussed on the prevalence of GERD in children with extra-oesophageal symptoms (Figure 3).

Respiratory symptoms were the most commonly studied extra-oesophageal symptom. Most articles focussed on a particular symptom or diagnosis such as asthma (six articles), ALTE (five articles), pneumonia (one article), bronchiectasis (one article) or general or multiple respiratory symptoms (two articles). ENT symptoms were the focus of three articles, and a further two articles evaluated dental erosion.

Asthma. Only one study meeting our inclusion criteria evaluated asthma in children with GERD, a large study by El-Serag and colleagues that used the administrative database at Texas Children’s Hospital. However, the data were based on the diagnoses made by several physicians and did not use a standardized definition of GERD or asthma, so caution is required in the interpretation of data from this study. The authors analysed retrospective data regarding medical diagnoses made in all patients with GERD (except those with cerebral palsy, mental retardation, tracheo-oesophageal congenital anomalies or congenital oesophageal stenosis) between 1996 and 2000. They examined records from 1980 children (older than 2 years; mean age 9.16 years) with a diagnosis of GERD and 7920 controls (children older than 2 years; mean age 8.64 years) without. The prevalence of diagnosed asthma in children with GERD
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Reference</th>
<th>Population size</th>
<th>Study design</th>
<th>Method of data collection</th>
<th>Definition of reflux symptoms</th>
<th>Definition of extra-oesophageal symptom</th>
<th>Prevalence of extra-oesophageal symptom in children with GERD</th>
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<tbody>
<tr>
<td>Respiratory symptoms</td>
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<tr>
<td>Asthma</td>
<td>El-Serag et al.¹²</td>
<td>1980 with GERD + 7980 controls</td>
<td>Association case-controlled study</td>
<td>Database</td>
<td>Physician diagnosis</td>
<td>Physician diagnosis</td>
<td>13.2% vs. 6.8% of controls (P &lt; 0.0001)</td>
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<tr>
<td>Pneumonia</td>
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<td>Bronchiectasis</td>
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<tr>
<td>ALTE</td>
<td>Tolia et al.¹⁰</td>
<td>173 with GERD + 169 controls</td>
<td>Association case-controlled study</td>
<td>Database</td>
<td>Physician diagnosis</td>
<td>Physician diagnosis</td>
<td>20% vs. 31% of controls (P &lt; 0.12)</td>
</tr>
<tr>
<td>General respiratory symptoms</td>
<td>Khalaf et al.¹⁵</td>
<td>42 with severe RI + 66 controls</td>
<td>Cross-sectional controlled study</td>
<td>Continuous recording of respiratory rate, heart rate, nasal air flow</td>
<td>RI &gt; 6, presence of feeding problems and response to anti-reflux measures</td>
<td>Respiratory distress syndrome defined by clinical features and positive chest radiograph</td>
<td>62% vs. 36% of controls (P = 0.02)</td>
</tr>
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<td>General respiratory symptoms</td>
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<tr>
<td>ENT symptoms</td>
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<tr>
<td>Sinusitis</td>
<td>El-Serag et al.¹²</td>
<td>1980 with GERD + 7980 controls</td>
<td>Association case-controlled study</td>
<td>Database</td>
<td>Physician diagnosis</td>
<td>Physician diagnosis</td>
<td>4.2% vs. 1.4% of controls (P &lt; 0.0001)</td>
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<td>Otitis media</td>
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<td>Dental symptoms</td>
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<tr>
<td>Dental erosion</td>
<td>Linnett et al.²⁸</td>
<td>52 with GERD + 52 healthy controls</td>
<td>Prospective controlled study</td>
<td>Dental examination/medical/dental records</td>
<td>Physician diagnosis</td>
<td>WHO criteria for caries</td>
<td>14% had erosion vs. 10% of controls (P &lt; 0.05)</td>
</tr>
<tr>
<td>Dental erosion</td>
<td>Ersin et al.²⁷</td>
<td>38 with GERD + 42 healthy controls</td>
<td>Cross-sectional controlled study</td>
<td>Questionnaire/dental exam</td>
<td>Physician diagnosis</td>
<td>WHO criteria for caries Eccles &amp; Jenkins index for erosion by GERD</td>
<td>76% had erosion vs. 10% of controls (P &lt; 0.0001)</td>
</tr>
</tbody>
</table>

ALTE, apparent life-threatening event; ENT, ear, nose and throat; GERD, gastro-oesophageal reflux disease; RI, reflux index (% of total time when pH < 4); WHO, World Health Organization.
Table 2. Prevalence of GERD in children with extra-oesophageal symptoms

<table>
<thead>
<tr>
<th>Symptom Reference</th>
<th>Population size</th>
<th>Study design</th>
<th>Method of data collection</th>
<th>Definition of extra-oesophageal symptoms</th>
<th>Diagnosis of reflux symptom</th>
<th>GERD prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory symptoms</td>
<td>Asthma</td>
<td>872 asthmatics + 264 controls</td>
<td>Cross-sectional controlled study</td>
<td>Questionnaire GINA classification</td>
<td>Physiological pH monitoring: reflux defined as a decrease in pH to &lt; 4 for at least 15 s</td>
<td>19.2% of asthmatics had a positive GERD symptom score vs. 8.5% of controls (odds ratio, 2.6, ( P &lt; 0.001 ))</td>
</tr>
<tr>
<td>Asthma</td>
<td>Barakat et al.</td>
<td>75 asthmatics + 25 controls</td>
<td>Cross-sectional controlled study</td>
<td>Medical history/physical examination</td>
<td>Presence of visceral sensitivity and symptoms consistent with GERD</td>
<td>39% of asthmatics demonstrated reflux on oesophagography, vs. 0% of controls (( P &lt; 0.05 ))</td>
</tr>
<tr>
<td>Asthma</td>
<td>Chopra et al.</td>
<td>80 asthmatics + 10 controls</td>
<td>Cross-sectional controlled study</td>
<td>Medical examination</td>
<td>Gastro-oesophageal reflux, defined as a decrease in pH to &lt; 4 for at least 15 s, occurred in 33% of asthmatics vs. 33% of controls with asthma vs. 16% of controls (( P &lt; 0.05 ))</td>
<td></td>
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<tr>
<td>Asthma</td>
<td>Hughes et al.</td>
<td>9 asthmatics + 7 controls</td>
<td>Cross-sectional controlled study</td>
<td>Medical examination</td>
<td>Oesophageal pH monitoring: reflux defined as a decrease in pH to &lt; 4 for at least 15 s</td>
<td>No significant difference between the two groups in number of reflex episodes or % of time pH &lt; 4</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Symptom</th>
<th>Reference</th>
<th>Population size</th>
<th>Study design</th>
<th>Method of data collection</th>
<th>Definition of extra-oesophageal symptoms</th>
<th>Diagnosis of reflux symptom</th>
<th>Prevalence of GERD in-patients with extra-oesophageal symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Debley et al.(^\d)</td>
<td>296 asthmatics + 1510 controls</td>
<td>Population-based, cross-sectional controlled study</td>
<td>Questionnaire</td>
<td>Physician diagnosed or a positive response to selected questions on the ISAAC questionnaire(^{67, 68})</td>
<td>Positive response to selected questionnaire questions</td>
<td>19.3% of adolescents with current asthma had GERD symptoms vs. 2.5% of adolescents without asthma ((P &lt; 0.001))</td>
</tr>
<tr>
<td>ALTE</td>
<td>Gorrotxategi et al.(^\d)</td>
<td>14 infants with ALTE + 10 controls</td>
<td>Cross-sectional controlled study</td>
<td>Medical examination</td>
<td>Defined using guidelines from NIH Consensus Development Conference on infant apnoea</td>
<td>24-h pH monitoring</td>
<td>RI = 5.614 in ALTE patients vs. 2.01 in controls (not significant)</td>
</tr>
<tr>
<td>ALTE</td>
<td>Kahn et al.(^\d)</td>
<td>20 infants admitted for ALTE + 10 controls</td>
<td>Cross-sectional controlled study</td>
<td>Medical examination</td>
<td>Physician diagnosis</td>
<td>Oesophageal pH monitoring</td>
<td>No significant difference between the two groups in terms of pH falls or duration</td>
</tr>
<tr>
<td>ALTE</td>
<td>Kahn et al.(^\d)</td>
<td>50 infants admitted for ALTE + 50 controls</td>
<td>Cross-sectional controlled study</td>
<td>Medical examination</td>
<td>Physician diagnosis</td>
<td>pH &lt; 4 for (\geq30) sec</td>
<td>No significant difference between the two groups in terms of pH falls</td>
</tr>
<tr>
<td>ALTE</td>
<td>Sacre and Vandenplas(^\d)</td>
<td>62 infants with ALTE + 378 controls</td>
<td>Cross-sectional controlled study</td>
<td>Medical examination</td>
<td>Physician diagnosis</td>
<td>24-h pH monitoring</td>
<td>42% of infants with ALTE had gastro-oesophageal reflux vs. 8.5% of controls</td>
</tr>
<tr>
<td>ENT symptoms</td>
<td>Contencin and Narcy(^\d)</td>
<td>8 patients consulting for laryngotracheitis + 6 controls</td>
<td>Cross-sectional controlled study</td>
<td>Medical examination</td>
<td>Physician diagnosis</td>
<td>Dual-channel pH monitoring. Pathological gastro-oesophageal reflux defined as RI &gt; 5.2%</td>
<td>62.5% of patients had pathological gastro-oesophageal reflux vs. 16.6% of controls</td>
</tr>
</tbody>
</table>

ALTE, apparent life-threatening event; ATS, American Thoracic Society; ENT, ear, nose and throat; GERD, gastro-oesophageal reflux disease; GI, gastrointestinal; GINA, Global Initiative for Asthma; ISAAC, International Study of Asthma and Allergies in Childhood; NIH, National Institutes of Health; RI, reflux index.
was twice that in controls (13.2\% vs. 6.8\%; \(P < 0.0001\)).

Five studies evaluated the presence of GERD in children with asthma. Four of the studies reported a higher prevalence of GERD in children with asthma compared with healthy controls. A study in paediatric outpatient clinics evaluated 872 children (aged 7–16 years) with asthma (according to the Global Initiative for Asthma classification) and 264 healthy controls. Using the GERD Questionnaire developed by Nelson and colleagues, the study showed that 19.7\% of children with asthma had a positive GERD symptom score compared with 8.5\% of controls (odds ratio 2.6, \(P < 0.001\)). The questionnaire was completed regardless of current asthma symptoms. A further questionnaire-based study showed that among 13 and 14-year-olds with asthma, 19.3\% had symptoms of GERD, compared with 2.5\% of those without asthma (\(P < 0.001\)). Another study showed the prevalence of gastrointestinal symptoms (investigated by endoscopy and abdominal ultrasonography) to be 65\% in children with a diagnosis of asthma and 16\% in healthy controls (\(P < 0.001\)). A scintiscan study of 80 children (age range 9 months–12 years) with asthma (defined as three or more episodes of reversible bronchospasm) and a small control population of just 10 healthy controls showed that 39\% of the children with asthma but none of the controls had reflux symptoms. However, this study evaluated just a single episode of postprandial reflux and therefore may not be a true indication of GERD. The smallest of the five studies investigated just nine children (mean age 15.2 years) with asthma according to the American Thoracic Society guidelines. Oesophageal pH monitoring revealed that three of the nine children with asthma (33\%) experienced reflux, compared with 4 of 7 healthy controls (57\%).

Estimates of the prevalence of GERD in children with asthma varied between 19.3\% and 65\%, giving a pooled sample-size-weighted average prevalence of 23.4\%. Estimates in controls varied between 0\% and 57\%, giving a pooled sample-size-weighted average prevalence of 3.8\%. The variation in the results is most probably related to the methodology used to identify GERD. The studies using an oesophageal pH probe or endoscope reported relatively high prevalence estimates (33–65\%), as did the study using scintigraphy (39\%), whereas the studies that used a questionnaire to assess GERD symptoms reported the lowest prevalence estimates (19.3\% and 19.7\%).

Alternative sources of variation in the data include the small sample sizes, the lack of standardized definitions for reflux and asthma symptoms, the
timing of the study in relation to the patients' symptoms, and the variation in age groups between the studies.

**Pneumonia.** Only one study meeting our inclusion criteria evaluated the prevalence of pneumonia in children with GERD. In the Texan study by El-Serag and colleagues described above, the prevalence of pneumonia in 1980 children with GERD was 6.3%, compared with 2.3% in a healthy control population of 7920 children ($P < 0.0001$).12 Again, standardized definitions were not used for the symptoms, and the temporal relation between the onset of pneumonia and GERD symptoms was not noted; it is therefore hard to draw firm conclusions from these data alone.

**Apparent life-threatening event.** A large study reported the prevalence of ALTE (an episode characterized by some combination of apnoea, colour change, marked change in muscle tone, choking or gagging, that is frightening to the observer) to be 20% in a sample of 173 infants (under 1 year of age) with GERD (diagnosed as a reflux index greater than 5% on extended pH monitoring). This was less than the prevalence among the 169 healthy controls (31%; $P < 0.12$).20 As this study was retrospective, it did not document the rate of ALTEs that occurred during reflux. A further four smaller studies reported the occurrence of GERD in infants (less than 1 year of age) presenting with ALTE, although no study established a temporal link. Three of these studies reported no significant difference in terms of reflux symptoms between infants who had experienced an ALTE and controls.21–23 However, the largest of the four studies evaluated 62 infants with episodes of paleness possibly suggestive of an ALTE.24 The results of the study showed that 42% of the 62 infants had abnormal pH-metry results, compared with 8.5% of the 378 control infants.

**Bronchiectasis.** The retrospective study by El-Serag et al. described above showed that the prevalence of bronchiectasis was 10-fold higher in children with GERD than in healthy controls (1% vs. 0.1%; $P < 0.0001$).12 It is hard to draw firm conclusions from these data alone, given the limitations of the study described above.

**General respiratory symptoms.** The two studies that investigated general or multiple respiratory symptoms in infants with GERD reported contradictory results. One database study showed that significantly fewer of the 173 infants (mean age 3.3 months) with GERD had respiratory symptoms (including wheezing, apnoea, aspiration, pneumonia, ALTE, and/or cyanotic episodes) than did the 169 controls (49% vs. 63%; $P < 0.01$).20 A smaller cross-sectional study of 42 patients with GERD and 66 healthy controls showed a prevalence of up to 62% for general respiratory symptoms in infants with GERD, which was significantly higher than that in healthy children ($P < 0.02$).25

**Ear, nose and throat symptoms.** In the retrospective study described above, sinusitis was present in 4% of children with GERD compared with only 1% of controls ($P < 0.0001$).12 Moreover, the prevalence of otitis media was significantly lower in children with GERD (2.1%) than in controls (4.6%; $P < 0.0001$) in the same study. No further data were found that confirmed this finding. A small prospective study of children (aged 2 months–7.5 years) being
evaluated for laryngotracheitis showed that 62% had pathological reflux, compared with 16.6% of controls.26

**Dental erosion.** Two studies reported considerably different values for the prevalence of dental erosion in children with GERD (14% and 76%). Both showed that the prevalence was higher in children with GERD than in healthy controls ($P < 0.05$).27, 28

**Other symptoms.** There were no studies meeting our inclusion criteria that evaluated the putative relationship between GERD in children and apnoea, cough, bronchitis, laryngitis, pharyngitis, functional recurrent abdominal pain, colic, rumination syndrome, cystic fibrosis or Sandifer’s syndrome.

**Pharmacotherapy of extra-oesophageal symptoms**

The impact of pharmacotherapy of GERD on extra-oesophageal symptoms was evaluated in three studies in children (Table 3). A short-term (4-week) study considering the effect of the prokinetic agent cisapride (in the presence of the histamine-2 antagonist ranitidine) on persistent crying in infants aged 0.5–8.2 months showed no advantage over placebo.29

A 12-week study also failed to show improvement in asthma symptoms following treatment with a proton pump inhibitor (PPI).19 However, a longer-term (6-month) study reported significant improvements in asthma symptoms in-patients receiving a PPI compared with control groups.30

**DISCUSSION**

**Summary of results**

Data from well-selected retrospective and prospective observational studies may suggest an association between GERD and asthma in children, and further possible associations with pneumonia, bronchiectasis, ALTE, laryngotracheitis, sinusitis and dental erosion. However, the paucity of large well-conducted controlled studies, the varying definitions of diseases used and the wide range of investigative techniques make it difficult to draw firm conclusions.

The impact on extra-oesophageal symptoms of treating GERD by pharmacological approaches varied between studies. PPIs may be beneficial in the control of childhood asthma, but further studies are needed to confirm this.

**Results in context**

**Prevalence of GERD in children with extra-oesophageal symptoms.** The reported prevalence of GERD in children with asthma ranged from 19.3% to 65%. This wide variation in prevalence estimates most likely reflects the small sample sizes, the differing definitions of asthma and GERD used in studies, the fact whether or not asthma symptoms were present during the investigations, the variety of age groups studied, and the differing techniques used to make a diagnosis. None of the included studies differentiated patients with allergic asthma; the impact of the proposed link between GERD and atopic conditions (discussed below) on the results was therefore not apparent. The calculated pooled sample-size-weighted average for these prevalence data (23.4%) is higher than that for the control data from the same studies (3.8%). In adults, the prevalence of GERD symptoms in-patients with asthma appears to be higher (59.2%) than that found for children in our analysis.9

Data included in this review suggest a possible association between laryngotracheitis and GERD in children. The prevalence of pathological reflux (defined as a reflux index greater than 5.2%) in children with laryngotracheitis (62.5%) is substantially higher than the previous estimates determining that 4–10% of adults with laryngeal disease have concomitant GERD.31

Previously reported estimates of the prevalence of GERD in the general paediatric population varied from approximately 2% to 25% depending on the symptoms evaluated.13 A population-based retrospective study estimated the prevalence of GERD in children under 5 years of age (mean age at diagnosis, 7.3 months) to be 0.91 per 1000 person-years.32 The broad range of reported prevalence estimates may be attributable to the lack of a uniform definition of symptoms and the methods of data collection. In the general adult population, a prevalence of 10–20% has been reported.33 Only one of the four studies included in our analysis that investigated GERD in children who had symptoms suggestive of an ALTE reported a prevalence value.24 The prevalence reported in this study (42%) is slightly higher than the figures reported by Nelson et al. and Dent et al.,13, 33 possibly suggesting that ALTE is associated with an increased prevalence of GERD;
<table>
<thead>
<tr>
<th>Reference</th>
<th>Population size</th>
<th>Study design</th>
<th>Definition of reflux symptoms</th>
<th>Definition of extra-oesophageal symptom</th>
<th>Drug and dosage</th>
<th>Outcome</th>
</tr>
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<tr>
<td>Khoshoo and Haydel</td>
<td>30</td>
<td>Investigator-blinded</td>
<td>24-h pH monitoring pH &lt; 4 for &gt;5% of the time</td>
<td>Asthma ≥ 3 episodes per year despite optimal treatment</td>
<td>Group A: esomeprazole (40 mg/day)/metoclopramide Group B: ranitidine (150 mg 3 times daily) Group C: control (fundoplication) All had previously had PPI/prokinetic for 1 year</td>
<td>Following 6 months’ treatment, group B had significantly more exacerbations than groups A and C</td>
</tr>
<tr>
<td>Jordan et al.</td>
<td>34</td>
<td>Randomized placebo-control</td>
<td>Oesophageal 24-h pH monitoring</td>
<td>Physician diagnosis of persistent crying</td>
<td>4 weeks treatment with ranitidine (3 mg/kg, 3 times daily) plus cisapride (0.2 mg/kg, 4 times daily)</td>
<td>Anti-reflux medications were not superior to placebo in treating infants with persistent crying Asthma symptoms scored by two questionnaires did not differ significantly between groups following treatment</td>
</tr>
<tr>
<td>Stordal et al.</td>
<td>38 with asthma</td>
<td>Randomized placebo-control</td>
<td>Questionnaire/RI ≥ 5 on 24-h pH monitoring</td>
<td>Physician-diagnosed asthma</td>
<td>Omeprazole 20 mg once daily or placebo for 12 weeks</td>
<td></td>
</tr>
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PPI, proton pump inhibitor; RI, reflux index.
however, further large controlled studies using a standardized definition are required to confirm this.

A recent study in adults showed a positive association between cough and acid reflux in a significant subgroup of patients with chronic cough. We did not identify any controlled studies that evaluated the association between GERD and cough in children. Nor did we identify any studies meeting our inclusion criteria that evaluated the putative relationship between GERD in children and apnoea, bronchitis, laryngitis, pharyngitis, functional recurrent abdominal pain, colic, rumination syndrome, cystic fibrosis or Sandifer’s syndrome, mainly because of the lack of a control group.

Prevalence of extra-oesophageal symptoms in children with GERD. The single study of asthma in children with GERD showed asthma to be more prevalent in these children than in healthy controls. However, as discussed above, there are several limitations to this study and so more studies are required to confirm this finding. Similarly, evidence from a systematic review of adult data and a prospective multicentre open cohort study show that the prevalence of asthma is higher in adults with GERD than in the general population, but it appears to be lower than in the study in children described in our review. We found that pneumonia was more prevalent in children with GERD (6.3%) than has been previously found in a large population-based trial (2%). The single study reporting the prevalence of ALTE in infants with GERD showed it to be lower than in controls. This suggests a lack of correlation between GERD and ALTE. Further large controlled prospective studies are required to confirm this result, but the findings are in agreement with previous data. Respiratory symptoms such as cough, wheezing and asthma have been reported to be more common in children with an inlet patch (a distinct area of ectopic gastric mucosa located in the proximal oesophagus) than in controls.

The large database study that found an association between GERD in children and sinusitis is supported by data from a systematic review of adult patients that showed a positive association between GERD and both sinusitis and laryngeal malignancy. The database study by El-Serag and colleagues also showed that otitis media was significantly less prevalent in children with GERD than in controls. There is no evidence in the literature for a protective mechanism, so it seems unlikely that GERD is protective against otitis. This result may therefore be a consequence of the weaknesses of this study, as highlighted above. Data from two studies that did not meet the inclusion criteria for our review because of the lack of a control group reported an association between acid reflux and otitis media in children.

Despite few studies meeting the inclusion criteria for our review because of their lack of control group, we found some support for the hypothesis that children with GERD have a significantly higher prevalence of dental erosion than healthy controls. The acidic nature of gastric reflux is thought to cause characteristic dental erosion, although both GERD and dental erosion have been associated with common modifiable risk factors such as consumption of sugary carbonated soft drinks, and not brushing teeth after every meal. A recent systematic review showed a strong association between the prevalence of GERD and dental erosion. The median prevalence of GERD in adults with dental erosions was 32.5%, while in paediatric patients with dental erosions it was 17%. However, a study in young adults (19–22 years old) reported that there was no association between dental erosions and GERD.

Pharmacotherapeutic data. We found possible support for an association between GERD and asthma in children from one long-term (6-month) pharmacotherapeutic trial of a PPI (esomeprazole, given in combination with metoclopramide), although two shorter term studies (including one randomized blinded trial) failed to show a significant improvement in asthma symptoms over placebo of either omeprazole, or ranitidine in combination with cisapride. In their study, Khoshoo and Haydel selected only patients with pathological reflux and not those with weakly acid reflux, which may have favoured a positive effect of the PPI. The variation in the recorded outcomes may be a result of the anti-reflux therapy chosen; the superior control of extra-oesophageal symptoms with PPIs compared with cisapride may correspond with a greater effectiveness of PPIs in providing relief from GERD. Alternative reasons for the variation in the results could include the symptoms studied, the disease definitions and methodology used, the dosing regimen, the length of study and the small sample sizes.

A large controlled trial in adults showed that acid inhibition led to only a small improvement in asthma
symptoms in adults with gastro-oesophageal reflux who had nocturnal episodes of asthma. In contrast, two recent meta-analyses found that PPIs failed to have a significant effect on chronic laryngeal symptoms that had been attributed to GERD in adult patients. Furthermore, a Cochrane systematic review of randomized controlled trials identified from the Cochrane Airways Group trial register evaluated the effects of GERD treatment on asthma. The majority of the studies focussed on adult patients but one looked at the effects of GERD treatment in adolescent patients. In agreement with our findings, the authors of the Cochrane review found that the interventions used and outcomes assessed were inconsistent between the 12 studies they reviewed. The authors concluded that in-patients with both asthma and GERD, treatment for GERD did not produce consistent improvement in asthma symptoms. A more recent Cochrane review reported that there was insufficient evidence to conclude that PPI treatment is beneficial for cough associated with GERD in adults and children.

Clinical implications

The lack of studies investigating the temporal relationship between GERD and extra-oesophageal symptoms makes it difficult to determine a causal relationship. Gastro-oesophageal reflux has previously been suggested to be a symptom of atopic disease. It is therefore possible that GERD may be secondary to atopic conditions such as asthma. Allergic exacerbation may cause wheezing, which in turn induces reflux through an increase in intra-abdominal pressure. A further consideration is that reflux could cause respiratory symptoms. The reflex theory postulates that the presence of acid in the oesophagus stimulates a vagally mediated bronchoconstriction. A large longitudinal study, conducted using the UK General Practice Research Database, showed that patients with asthma had an increased risk of developing GERD, but that patients with GERD did not have an increased risk of developing asthma. Future longitudinal studies would help in clarifying any possible causal relationship.

Our results suggest that the prevalence of GERD may vary according to the methodology used to diagnose it. Further to clinical diagnoses, the most commonly used technique was pH-metry. However, it has the limitation of being unable to detect non-acid reflux and this is one reason why several other techniques have been used to investigate GERD. Simultaneous dual channel oesophageal pH monitoring has been shown to identify reflux in a further 46% of children who would otherwise have been falsely presumed to have normal reflux parameters. Multi-channel intraluminal impedance is of use in the detection of non-acid or weakly acid reflux events. Radionuclide scanning can be used to detect episodes of gastro-oesophageal reflux and pulmonary aspiration occurring during or shortly after meals. Its reported sensitivity for micro-aspiration is relatively low, but the infrequency of aspiration events may explain a negative test. Nuclear scintigraphy is not recommended in the routine diagnosis and management of GERD in infants and children but may be of use for detecting non-acid reflux events. Oesophageal ultrasonography is a favourable option in children because of its non-invasive nature but at present its use as a diagnostic tool for GERD is limited. It is therefore necessary for physicians to consider the variability between techniques when evaluating extra-oesophageal manifestations of GERD in the paediatric population.

Further research is required to confirm the data reviewed in this study that suggest an association between GERD and several extra-oesophageal symptoms in children. GERD may be a possible underlying cause or aggravating factor in children with asthma and other respiratory symptoms. PPIs have been used for both the diagnosis and treatment of extra-oesophageal manifestations of GERD in adults, with varying success. Despite a high proportion of studies showing abnormal reflux in-patients with asthma, empiric PPI therapy is unlikely to be an effective approach. Instead, long-term anti-reflux therapy should be used only for those with persistent refractory asthma. Today, there is no evidence to recommend the use of anti-reflux medication in-patients presenting only with respiratory symptoms and without an objective diagnosis of GERD or evidence of temporal relationship between reflux and the respiratory event. Further data are required to confirm the usefulness of anti-reflux therapies for managing extra-oesophageal symptoms in GERD in the paediatric population.

Strengths and limitations

Only one other systematic review has assessed the prevalence of extra-oesophageal symptoms and their
relationship with GERD in infants and children. Our review is the first systematic review to explore the relationship between a broad range of extra-oesophageal symptoms and GERD in children. There were a number of limitations to our analysis. Very few available studies included a healthy control cohort, which limited the number of studies that could be included in our review. To gain a better understanding of whether extra-oesophageal symptoms are more prevalent in patients with GERD, and vice versa, we have made some comparisons with prevalence estimates from the general population. However, it is not ideal to draw comparisons between different population groups. Several studies did not explain how the GERD or extra-oesophageal conditions were diagnosed. As a result, there is likely to be variation in the definitions used and in the severity of illness, which makes direct comparisons of results difficult. Moreover, the lack of a consistent definition of GERD may have caused some patients to be falsely presumed to have GERD, resulting in inaccurate estimations of prevalence. The broad range in reported prevalence is probably the result of referral bias to centres with specialized interest, the sample size, or the technique used to make the diagnosis. A further consideration is that, because of the small number of studies that met our inclusion criteria, a substantial proportion of our data came from a single study that investigated multiple symptoms in children with GERD. Therefore, the limitations of the study by El-Serag and colleagues described above may have skewed the results of this review. Variations between the studies are also likely to have had an impact on the results from the pharmacotherapeutic trials; the studies varied in terms of the combinations of drugs used, the dosing regimens, the length of treatment and the symptoms studied.

Conclusions and future work

This review presents retrospective evidence from the literature that many children and infants with reflux symptoms may also have extra-oesophageal symptoms. It highlights the need for further well-designed case-controlled trials, using standardized techniques of investigation, a standardized definition of GERD (such as the Montreal Definition or the new paediatric definition of GERD1, 11) and standardized definitions of the extra-oesophageal symptoms. Future trials of anti-reflux therapies should be randomized controlled trials with appropriate control groups and make use of newer techniques such as Multichannel impedance pH monitoring so that clinically useful conclusions may be drawn. Longitudinal studies assessing the temporal relationship between GERD and extra-oesophageal symptoms in children are also needed.

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