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Prevalence of Gastroesophageal Reflux Disease Symptoms in Infants and Children: A Systematic Review

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ABSTRACT

Objectives: Gastroesophageal reflux disease (GERD) is defined as gastroesophageal reflux causing troublesome symptoms or complications. In this study we reviewed the literature regarding the prevalence of GERD symptoms in infants and children.

Methods: Databases of PubMed, EMBASE, and Cochrane were systematically searched from inception to June 26, 2018. English-written studies based on birth cohort, school-based, or general population samples of ≥ 50 children aged 0 to 21 years were included. Convenience samples were excluded.

Results: In total, 3581 unique studies were found, of which 25 studies (11 in infants and 14 in children) were included with data on the prevalence of GERD symptoms comprising a total population of 487,969 children. In infants (0–18 months), GERD symptoms are present in more than a quarter of infants on a daily basis and show a steady decline in frequency with almost complete disappearance of symptoms at the age of 12 months. In children older than 18 months, GERD symptoms show large variation in prevalence between studies (range 0%–38% of study population) and overall, are present in $>10\%$ and in 25% on respectively a weekly and monthly basis. Of the risk factors assessed, higher body mass index and the use of alcohol and tobacco were associated with higher GERD symptom prevalence.

Conclusions: This systematic review demonstrates that the reported prevalence of GERD symptoms varies considerably, depending on method of data collection and criteria used to define symptoms. Nevertheless, the high reported prevalence rates support better investment of resources and educational campaigns focused on prevention.

Key Words: children, gastroesophageal reflux disease, prevalence, symptoms, systematic review

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What Is Known

- Gastroesophageal reflux disease is defined as gastroesophageal reflux causing troublesome symptoms or complications.
- Over the past decades, gastroesophageal reflux disease has become more prevalent in adults and the same trend appears to be also ongoing in children.

What Is New

- Through systematic review of current literature, this study provides an overview of the prevalence of gastroesophageal reflux symptoms in infants and children.
- Reported prevalence of gastroesophageal reflux disease symptoms varies considerably, depending on method of data collection and criteria used to define symptoms.

Gastroesophageal reflux (GER), the retrograde flow of gastric contents into the esophagus, is a normal physiologic process occurring several times a day. Gastroesophageal reflux disease (GERD) is defined as a condition that develops when GER causes troublesome symptoms and/or complications (1). Although reflux occurs physiologically at all ages, there is also a continuum between physiologic GER and GERD, leading to different manifestations and complications depending on individual sensitivity and perception.

Few large population-based studies have described the epidemiology of GERD in children and most studies focus on the prevalence of GERD in specific groups. Comparison among studies is limited by the great heterogeneity in ways how studies define GERD (2). This is further complicated by the absence of a criterion standard diagnostic tool for GERD in children. Measuring symptoms is far easier to achieve on a large scale than the cumbersome physiological tests required to confirm if GERD is really present. As such, the most widely adopted assessments of the prevalence of GERD are based on symptoms only. In adults, estimated prevalence rates of GERD symptoms vary widely among different geographical areas and definitions used, ranging from 2.5% in China to 51.2% in Greece and in general, being the lowest in East Asia (3). Over the past decades, GERD has become more prevalent in adults and the same trend appears to be also ongoing in children. It is, however, unclear whether this reflects increasing case identification, or increases in other conditions that promote GERD, such as increased obesity rate, smoking, and dietary habits (4,5). Systematic analysis of studies that report on the epidemiology of GERD is important to

discover risk factors for the condition and to identify areas that warrant further research. In this study, we therefore aimed to systematically review the literature to report the prevalence of GERD-related symptoms and the criteria used to define them in infants and children.

METHODS

Search Strategy and Study Selection

A systematic literature search consisting of text and medical subject heading terms was used to perform a search of the PubMed, EMBASE (from 1947) and Cochrane databases up to June 26, 2018. In addition, reference lists of review articles and included studies were searched. The full search strategy is provided in Supplemental File 1 (Supplemental Digital Content 1, <http://links.lww.com/MPG/B579>).

Assessment of Study Eligibility

A 2-stage screening process was performed independently by 2 reviewers (M.S. and E.G.). At first, titles and abstracts were screened for eligibility. Studies were included if data on prevalence of GERD-related symptoms were defined including one of the following: heartburn and/or regurgitation of any severity or compatible symptoms adjudged by a clinician or according to any GERD symptom questionnaire or diary. Studies based on birth cohort, school-based or general population samples of ≥ 50 children aged 0 to 21 years were eligible. Studies that recruited convenience samples, such as those attending a health care professional for a scheduled regular health check-up, were only eligible when there was no specific medical indication for the visit. Studies in a language other than English were excluded. A recursive search was additionally performed using the bibliographies of all included studies.

Quality Assessment

A purpose-designed tool developed by Korterink et al (6), composed of a scale for quantitative studies (7) and a guideline for the evaluation of prevalence studies (8), was used to assess study quality. Studies were rated for how they met all criteria with no (–), partial (+/–), or yes (+).

Data Extraction and Analysis

As the manifestation of GERD is known to vary by age (9,10), data extraction was separated for infants (age 0–18 months) and children (age >18 months–21 years). As children over the age of 8 years are considered to be able to reliably self-report their symptoms, we attempted to stratify symptom prevalence data for children younger than 8 years of age and older children. The prevalence of (individual) GERD symptoms according to proposed risk factors, which were chosen a priori based on previous meta-analysis in adults (11). Meta-analysis methods were used to estimate the pooled prevalence of GERD symptoms were possible. Data were pooled when available for >2 studies, using either a fixed- or random-effect model according to heterogeneity (ie, $I^2 > 50\%$). Otherwise ranges were provided. In order to assess whether a more stringent definition of GERD symptoms impacted on prevalence, we pooled data from those studies that required a symptom frequency of at least daily, weekly, or monthly. Calculations were performed according to methods of Neyeloff et al (12), using a purpose-designed Microsoft Excel spreadsheet (Creative Commons Attribution 3.0 Unported [CC BY 3.0]).

RESULTS

Study Selection

After removal of duplicates, 3581 unique studies were identified of which 95 studies remained after title and abstract screening. Twenty-five studies fulfilled our inclusion and exclusion criteria (Fig. 1). No additional studies were identified through bibliographic review of included studies. Study characteristics including details of symptom frequency and duration required to meet criteria for GERD symptoms are described in Supplemental File 2 (Supplemental Digital Content 2, <http://links.lww.com/MPG/B580>).

Methodological Quality Assessment

Quality scores of all individual studies are overviewed and listed in Supplemental File 3 (Supplemental Digital Content 3, <http://links.lww.com/MPG/B581>). Reasons for limited study quality mainly considered: incomplete reporting of results ($n = 20$ studies), absent or incomplete description of analytic methods ($n = 18$), potentially inappropriate method of subject selection ($n = 9$), and study population not matching target population ($n = 9$).

Studies in Infants

Study Characteristics

Eleven studies comprised a total study population of 8553 infants (age 0–18 months). Studies originated from 5 different countries ($n = 6$ United States of America (13–18), $n = 4$ [Asia], ($n = 2$ Indonesia (19,20) and $n = 1$ each from Thailand (21) and Japan (22)), $n = 1$ from Europe [Italy] (23). Study cohorts consisted of infants attending well-baby clinics for their regular health check-ups or immunization ($n = 5$) (18,19,21–23). In 2 studies, parents were recruited via online survey panels (13,14) and in 1 study via a pediatric practice research network (17). Three studies were birth cohort studies (15,16,20). Eight studies used purpose-designed questionnaires or symptom diaries completed by parents. Other methods used were face-to-face interview ($n = 2$) (19,21), and a combination of questionnaire and interview ($n = 1$) (22).

Prevalence of Gastroesophageal Reflux Disease Symptoms

Four studies had a cross-sectional design, providing an overall prevalence of GERD symptoms in infants (13,14,18,23). Of these studies, 2 used the Rome III/IV criteria (13,14) for infant regurgitation, 1 the composite I-GERQ-R symptom score (18) and 1 a combination of clinical chart review and symptom record (23). The overall pooled prevalence of GERD symptoms was 26.9% (95% confidence interval [CI] 20.1–33.7, $I^2 = 6.83$) and ranged from 23.1% to 40.0%, with highest prevalence reported by the study using the I-GERQ-R (18).

Seven studies were prospective cohort studies, providing prevalence of GERD symptoms in the study population at different time points up to the age of 13 months (16,17,19–22). Five studies provided data on prevalence of daily regurgitation, showing a decrease in symptom prevalence with increasing age (Fig. 2) (17,19–22). Van Howe and Storms (16) prospectively assessed GERD symptoms using the I-GERQ-R with a cut-off ≥ 16 . They found prevalence to decrease from 25.5% at the age of 1 month to 2.9% at the age of 6 months. Chen et al (15) prospectively assessed “reflux” symptoms by asking the mothers if reflux was present

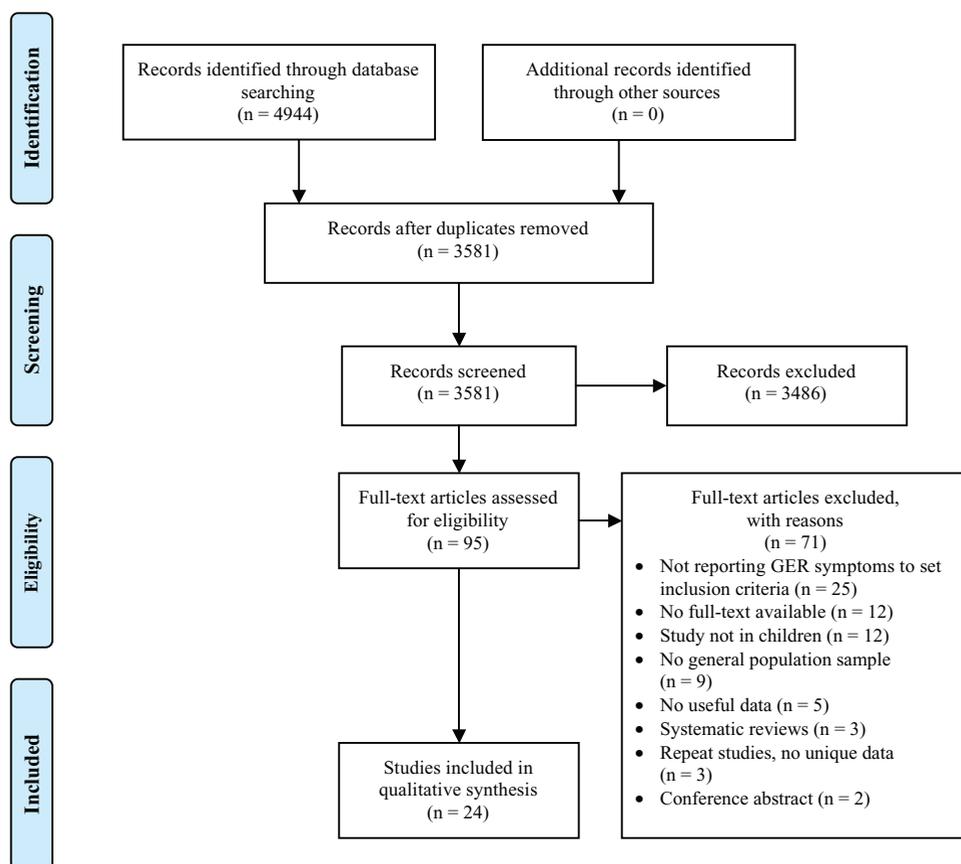


FIGURE 1. Study flow chart (search date 22-11-16, updated 26-06-18). GER = gastroesophageal reflux.

during the past 2 weeks. They found reflux symptoms to decrease from 9.2% at the age of 1 month to 1.6% at the age of 12 months.

Prevalence According to Proposed Risk Factors

Age, Sex, and Body Mass Index

One study assessed the influence of birth weight on GERD symptom prevalence and found a higher prevalence in infants with a birth weight <2500 g (30.6% vs 22.9%, $P < 0.001$) (23). Based on one study, sex was not associated with a difference in GERD symptom prevalence (compared to female sex, relative risk [RR] = 1.21, 95% CI 0.97–1.58) (15). None of the included studies assessed the influence of any of the other a priori proposed risk factors.

Mode of Feeding

Five studies assessed the influence of different feeding modes. Of these, 1 found a significantly lower proportion of infants (<6 months of age) to regurgitate on a daily basis in the group that was exclusively versus partially breast-fed (20). According to Chen et al, combinations with formula feeding showed a statistically significant risk for reflux (bottled human milk plus formula feeding (multinomial regression analysis: RR = 2.19, 95% CI 1.11–4.33; formula feeding: RR = 1.95, 95% CI 1.39–2.74; and mixed breast-feeding plus formula feeding: RR = 1.59, 95% CI 1.40–2.42) compared to direct breast-feeding. Addition of solid food was not protective (RR = 1.21, 95% CI 0.86–1.70). None of the other studies reported a significant difference in GER prevalence according to mode of feeding (21–23).

Studies in Children

Study Characteristics

Fourteen studies reported data on children, comprising a total study population of 479,417 children. Studies originated from 10 different countries (n = 5 Asia [Iran (24), Israel (25), Russia (26), Japan (27), and Thailand (28)], n = 5 USA (29–33), n = 3 Europe [Italy (34), Norway (35), and Ireland (36)], and n = 1 from Australia (37)). Twelve studies considered general (school-based) population samples, of which 1 study also included children attending scheduled immunization, well-child, and school screening examinations (33). One study from Israel included all candidates for military service (25) and 1 study from Japan included children of employees of a tertiary referral hospital (27). All except 1 study used a (purpose-designed) questionnaire to assess for GERD symptoms. Nine studies comprised a study population of children of 8 years and older. In 7 of these questionnaires were filled out by the children themselves with (36) or without help from the parent, and in 1 study by the parents only (37). Five studies comprised a study population including a mixed population of children older than or younger than 8 years (24,27,30,33,34). Of these, 2 studies used a proxy-reported questionnaire in combination with a child-reported questionnaire for children older than 10 years (30,33) and in the other study, questionnaires were filled out by the child with help of the parents regardless of the child's age (27). The other 2 studies did not provide information on method of data collection in sufficient detail (24,34). One study used a combination of a symptom questionnaire, chart review, and physical examination (25).

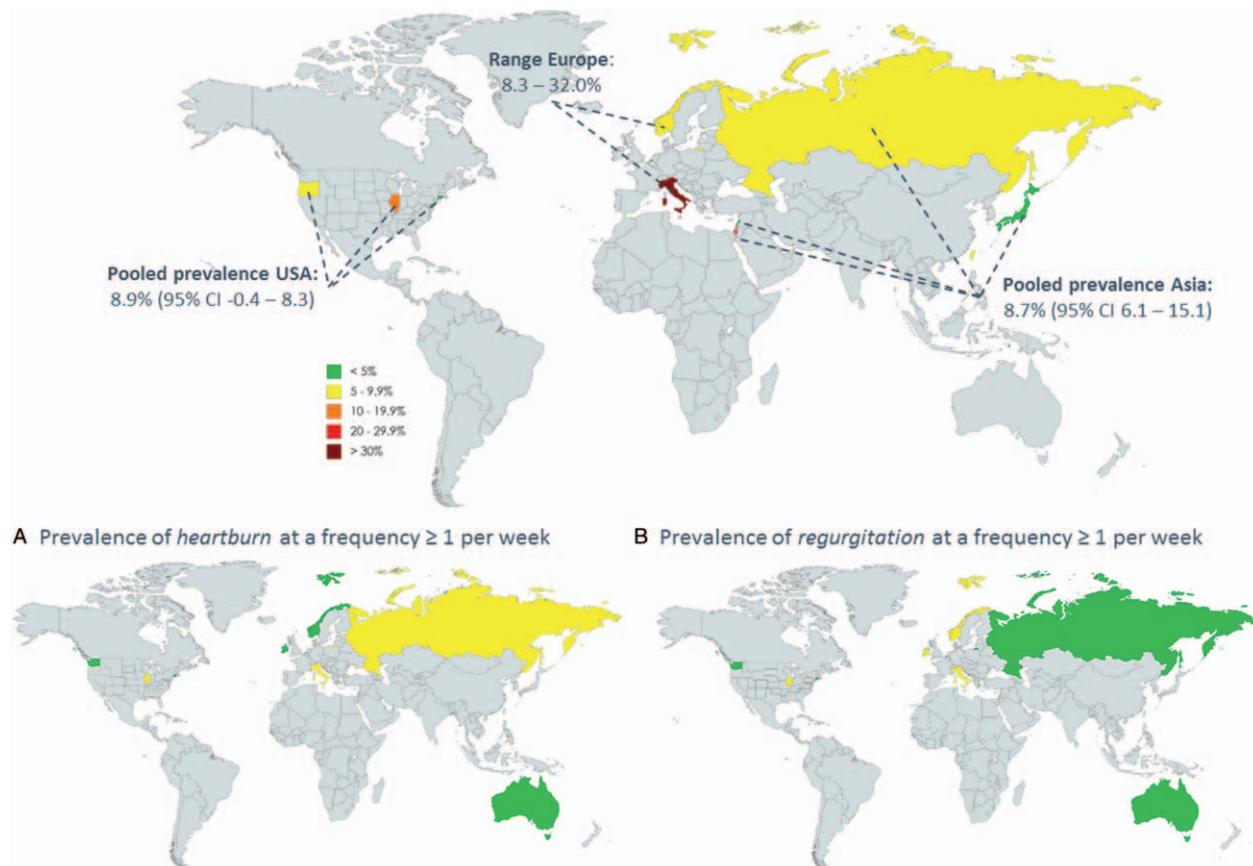


FIGURE 2. Prevalence of gastroesophageal reflux disease symptoms worldwide using symptoms at a frequency of once a week or more. A and B, The worldwide prevalence of individual gastroesophageal reflux symptoms of regurgitation and heartburn. Prevalences are pooled when data were available for >2 studies, otherwise ranges are provided.

Prevalence of Gastroesophageal Reflux Disease Symptoms

Of the 5 studies including both children younger and older than 8 years, 2 did not report prevalence data stratified for age. The 3 studies that did stratify for age, respectively used a cut-off age <10 (27,30) and <11 years (24). We therefore pooled data using a cut-off of <10 years and ≥10 years old. Data of studies using no or another cut-off are presented descriptively.

Age <10 Years (n = 3 Studies)

Okimoto et al (27) reported an overall prevalence of weekly GERD symptoms in children of 3.2% and did not specify prevalence of individual GERD symptoms. The other 2 studies did not report on overall prevalence, but found a prevalence of weekly regurgitation of respectively 0.9% and 2.3% and of weekly heartburn 0.5% and 1.8% (30,37).

Age ≥10 Years (n = 9 Studies)

Based on 8 studies, pooled prevalence of weekly GERD symptoms according to the criteria used by the authors to define their prevalence was 10.1% (95% CI 5.1–15.1%, $I^2 = 24.35$).

The lowest prevalence was 0.2% in a study conducted in Israel, where all candidates for military service were surveyed and prevalence was reported based on the occurrence of GERD symptoms >3 times a week, during 3 consecutive months (25). The

highest prevalence was 18.8%, reported in a study from the USA that assessed symptoms using a purpose-designed symptom questionnaire amongst high school children (31). Seven studies reported data for weekly heartburn or regurgitation symptoms individually, with a pooled prevalence of respectively 6.0% (95% CI 3.6–8.4%, $I^2 = -63.14$) and 6.1% (95% CI 4.2–7.9%, $I^2 = -62.60$). Nelson et al (30) was the only study using both proxy- and self-reported symptom assessment and they found higher symptom prevalence when self-reported compared to when proxy-reported (heartburn 5.2% vs 3.5%, regurgitation 8.2% vs 1.4%). Prevalence of daily and monthly symptoms is presented in Table 1.

No Age Stratification Applied (n = 2 Studies)

Pashankar et al (33) and Quitadamo et al (34) included children with an age ranging from respectively 2 to 18 years and 7 to 16.9 years and did not stratify prevalence data for age (33,34). Pashankar reported an overall prevalence of weekly GERD symptoms of 2% (regurgitation 4% and heartburn 3%). Quitadamo reported an overall prevalence of weekly GER symptoms of 32% (regurgitation 7.8% and heartburn 8.5%).

Prevalence According To Proposed Risk Factors

Ethnicity, Age, Sex, and Body Mass Index

The (pooled) prevalence of GERD symptoms in children (age >18 months) according to geographical study location is provided in Figure 3. One study evaluated the effect of

TABLE 1. Pooled prevalence of gastroesophageal reflux disease symptoms according to criteria used to define their presence and frequency in children ≥10 years

	Studies (n)	Subjects (n)	Pooled prevalence (%)	Range (%)	95% CI	I ² (%)
Overall GER symptoms						
Daily symptoms	0					
Weekly symptoms	8	474,618	10.1	0.2–18.8	5.1–15.1	24.35
Monthly symptoms	2	1792	NA	22.1–38.7	NA	NA
Heartburn						
Daily symptoms	2	1792	NA	0.7–0.9	NA	NA
Weekly symptoms	7	8763	6.0	3.0–11.0	3.6–0.8	–63.14
Monthly symptoms	2	1792	NA	16.9–22.4	NA	NA
Regurgitation						
Daily symptoms	2	1792	NA	0.7	NA	NA
Weekly symptoms	7	8763	6.1	2.9–8.8	4.2–7.9	–62.60
Monthly symptoms	2	1792	NA	8.5–21.4	NA	NA

CI = confidence interval; NA = not applicable; GER = gastroesophageal reflux.

Not applicable indicates too few studies to perform random effects model to pool prevalence rates and assess heterogeneity.

ethnicity on overall and individual GERD symptoms and did not identify a significant relationship (31). Four studies assessed the influence of sex on weekly GERD symptoms (25,26,28,36). Although 1 study reported a significant higher prevalence of overall GERD symptoms ($P=0.0059$), and of heartburn specific in girls ($P=0.007$) (28), none of the other studies identified a significant influence of sex on symptom prevalence. Four studies evaluated the influence of body mass index (BMI) (25,26,33,34), of which 3 found a significant association between higher BMI and overall GERD symptoms (25,26,33) (1 study no raw data provided (25)). Two studies evaluated the influence of BMI on prevalence of heartburn, epigastric pain, and regurgitation. Results were conflicting, with 1 study reporting a significantly higher prevalence of epigastric pain ($P=0.004$) and regurgitation ($P=0.008$) in patients with obesity (34) and the other reporting no differences based on BMI (36). In 3 studies, prevalence of GERD symptoms was stratified for age (24,27,30). Two of these studies found a trend toward higher prevalence in adolescents (ie, age >10 years) compared to younger children (24,27), whereas the third study reported higher symptom prevalences in the younger children in the cohort (30).

Smoking and Alcohol

One study evaluated the effects of smoking and alcohol use on overall GERD symptoms and found a trend toward higher symptom prevalence in those patients who smoked or consumed alcohol, albeit not statistically significant (26). Three studies evaluated the influence of smoking and alcohol on individual GERD symptoms in children aged 10 years or older (30,32,36). All studies found a significant association between smoking and heartburn, whereas smoking was reported to be associated with regurgitation in only 2 studies (32,36). A significant association between alcohol use (specified as >10 units per week in 1 study) in 2 studies (32,36), whereas in 1 other study no significant associations were found (30). In the one study that performed multivariate analysis, none of the associations remained significant (36).

Use of Nonsteroidal Anti-inflammatory Drugs

Only one study evaluated the effect of non-steroidal anti-inflammatory drug use on symptom prevalence and reported a trend toward higher prevalence of heartburn, albeit not being statistically

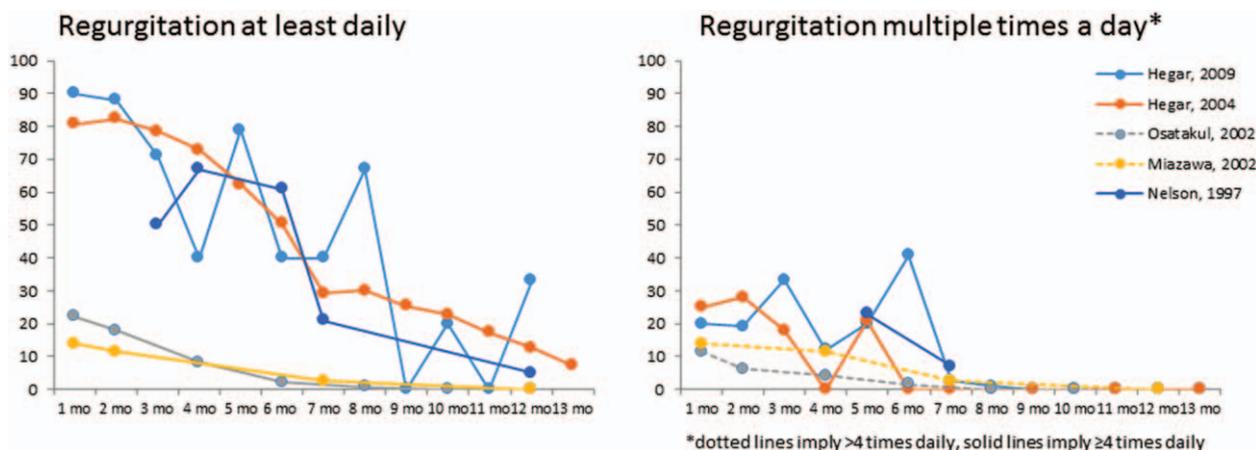


FIGURE 3. Prevalence of regurgitation in infants (age 0–13 months) using symptoms at a frequency of at least daily. CI = confidence interval.

significant (univariate analysis). Data on a relationship with regurgitation symptoms were not reported (32).

DISCUSSION

This is the first study to systematically describe the worldwide epidemiology of GERD symptoms in infants, children, and adolescents. We assembled data from 24 studies, of which 10 reported data on the prevalence of GERD symptoms in infants and 14 in older children, comprising a total population of more than half a million children. As previously reported, GERD symptoms are present in more than a quarter of infants on a daily basis and show a steady decline with increasing age. In older children, GERD symptoms are present in >10% of children on a daily and in a quarter of children on a monthly basis.

Previous studies in adults have shown remarkable geographic differences in GERD prevalence, with trends toward higher prevalence in North America and Europe when compared to Asia. Although global variation in prevalence of GERD symptoms may also be present in children, no firm conclusions can be drawn upon the included studies in the present review.

In line with findings in adults, we did not find a firm association between gender and prevalence of GERD symptoms in infants, nor in older children (3,25,28,38–41). Results on the influence of mode of feeding on GERD symptom prevalence in infants were conflicting, with some studies reporting no influence, and others demonstrating that breast-fed infants are less likely to experience regurgitation suggesting that direct breast-feeding is a protective factor against reflux (15,20). A recent study examining the monthly incidence of GERD in exclusively breast milk fed infants from ages 2 to 6 months failed to show an association between feeding mode and reflux incidence, but this analysis was limited by a small number of reported GERD cases (42). Based on expert opinion, current guidelines recommend to encourage breast-feeding in infants with physiological GER, but indicate that for infants with significant complaints to add thickeners to pumped breast milk (43). To provide appropriate guidance, further prospective studies about the differential effects of different feeding modes on infant health and GERD symptoms are needed.

Although none of the studies included in this review performed analysis for potential confounders, overall, in line with adult data, obesity, alcohol use, and smoking were associated with GERD symptoms (11). Recent evidence suggests that GERD in some subjects is a chronic, potentially life-long condition that begins in childhood and several studies suggest that the longer the duration of GERD symptoms, the higher the risk of persisting GERD symptoms and long-term sequelae such as Barrett esophagus and esophageal adenocarcinoma (9–14). The findings of our study therefore support implementation of preventive programs and surveillance and/or screening strategies to reduce prevalence of risk factors such as alcohol use and smoking that are, at least to some extent, modifiable.

This study has several strengths and limitations. We were the first to study the epidemiology of GERD symptoms in children worldwide and we provided a detailed and systematic review of published literature. We included studies reporting data on children aged 0 to 21 years to cover the transition from adolescence into adulthood and bridge the gap with adult literature. We limited our selection to studies including to general population samples, thereby excluding convenience samples to increase generalizability of data. Studies that used diagnostic disease codes were not considered in the present review, because they have the potential for multiple error sources including the amount and quality of information at admission, communication among patients and providers, and the clinician's knowledge and experience with the illness. Authors of original manuscripts were contacted to obtain

additional data when needed and to check for potential duplicate cohorts with extended follow-up. A limitation of this study is that we used an English-language restriction in performing our literature search and potentially relevant articles may therefore have been excluded. The majority of included studies were conducted in the USA or Asia, showing a paucity or lack of data from other geographical regions. Interpretation of results was hampered by significant heterogeneity of included studies suggesting lack of precision, which may be result of methodological differences, or other demographic or cultural differences in study populations. To reduce this effect, random effect models were used for meta-analyses. Unfortunately due to the limited number of studies identified and the great diversity in selected age groups among studies, we were unable to perform meta-analyses on single or narrow age groups nor to systematically analyze the effect of proposed risk factors on symptom prevalence.

To enhance the comparability between future studies, a consensus on how to best measure GERD symptoms in different age groups needs to be established first. Based upon consensus statements, in epidemiological studies in adults, GERD may be defined as mild symptoms occurring on 2 or more days per week, or moderate-to-severe symptoms occurring on 1 or more days per week (a threshold often considered troublesome by patients) (44). Such a recommendation for the pediatric population is, however, lacking. Typical symptoms as described in adults (eg, heartburn, chest pain) cannot readily be assessed in preverbal infants and children. Moreover, it is the parents who interpret GERD symptoms as being troublesome and associated with impaired quality of life or not. In line with this finding, Hua et al (45), reported cumulative incidence of GERD (present if reflux ever occurred) in infants to be 23% when parents reported, and only 14% when confirmed by a doctor. A symptom-based definition of GERD with an age-tailored symptom specification and frequency threshold sufficient to impair quality of life may allow a realistic assessment of GERD prevalence and incidence. To come to such a definition, a greater understanding of GERD symptoms based on patients' and parents' descriptors and pragmatic tools to measure them are needed. In this, it will be important to pay emphasis to patient- versus proxy-reported symptoms and quality of life indices as discrepancy between patient- and proxy-reporting has been demonstrated earlier. As children from the age of 8 years onwards have the ability to reliably self-report their symptoms, an appropriate approach may well be to tailor definition and diagnosis to infants and children younger than 1 and 8 years respectively, and adolescents. In summary, this systematic review demonstrated that the prevalence of GERD symptoms varies considerably, depending on method of data collection and criteria used to define symptoms. True estimates of the extent of GERD symptoms in infants and children may make it easier to differentiate to what extent symptoms can be considered part of normal physiology, or point to the presence of pathological GERD or other underlying disease. This may enhance the usability of research findings for clinical practice. Longitudinal data could prove particularly valuable for the study of the progression of GERD from infancy to adulthood and identification of potential risk factors that result in complications. The reported prevalence rates support investment of resources and educational campaigns focused on prevention and the search for a better diagnostic tool.

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