National Collaborating Centre for Women's and Children's Health

Final version

Gastro-oesophageal reflux disease in children and young people: Appendix I

Gastro-oesophageal reflux disease: recognition, diagnosis and management in children and young people

Nice Guideline 1

Appendix I: Evidence Tables

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Final version

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Contents

Appendix I: Evidence tables

GER and GERD are equivalent acronyms to GOR and GORD that reflect the American English spelling of oesophagus as esophagus. These terms are used in this appendix where they have been used in the studies contributing to the evidence base for the guideline.

I.1 What is the natural history of overt GOR?

Study details	Participants	Methods	Outcomes and results	Comments
Full citation Ruigomez,A., Wallander,M.A., Lundborg,P., Johansson,S., Rodriguez,L.A., Gastroesophageal reflux disease in children and adolescents in primary care, Scandinavian Journal of Gastroenterology, 45, 139-146, 2010 **Ref Id** 238295 **Country/ies where the study was carried out** UK **Study type** Retrospective cohort **Aim of the study** To determine the prevalence and incidence of a diagnosis of GERD in children and adolescents in UK primary care, and to assess specific comorbidities that are associated	**Sample size** GERD cohort: n = 1700 Control cohort: n = 4977 **Characteristics** Age of subjects 1 to 17 years GERD cohort: 55% were adolescents aged 12-17 years Male, n/N (%) 857/1700 (50.4) Race Not reported **Inclusion Criteria** GERD cohort Aged 1 to 17 years GERD diagnosis based on Read codes for gastro-oesophageal reflux, reflux esophagitis, esophageal inflammation and heartburn. Did not include non-specific symptoms such as epigastric pain. Control cohort Randomly selected from same source population (matched by age and sex) Aged 1 to 17 years	**Details** Study setting UK primary care Regurgitation definition used in study GERD: based on Read codes for gastro-oesophageal reflux, reflux esophagitis, esophageal inflammation and heartburn. Did not include non-specific symptoms such as epigastric pain. Method of obtaining data on regurgitation Data extracted from The Health Improvement Network (THIN) UK primary care database - a computerised medical research database of 2.3 million patients. Length of follow-up (if relevant to study design) All individuals in the source population were followed from 1 January 2000 until the earliest occurrence of one of the following endpoints: 1) case detection (i.e. Read code for GERD); 2) reaching the age of 18 years; 3) death; 4)	**Results** The median or mean average age (plus range or SD) at which overt reflux was first reported Not reported The median or mean average age (plus range or SD) age at which overt reflux was most frequent Not reported The reported maximum daily frequency of reflux (number of episodes of regurgitation) Not reported The mean frequency (SD) of regurgitation per day with increasing age *Reported as prevalence (%) of GERD in the study population of children and adolescents during 2000 to 2005 Age 1 yr Male: 2.2 Female: 1.9	**Limitations** - Based on electronic medical records across a number of GP practices, so variation tests and treatments - Only 15.3% of GERD cohort had a record of a formal diagnostic test being undertaken - None of the children in the control cohort had been tested for GER - Indirectness: this study examines GERD not regurgitation **Other information**

Study details	Participants	Methods	Outcomes and results	Comments
with a diagnosis of GERD, such as congenital and neurological disorders **Study dates** January 2000 to December 2005 **Source of funding** AstraZeneca R&D, Sweden.	Without diagnosis of GERD **Exclusion Criteria** Pregnant adolescents	end of study period (31 December 2005) Sample size calculation Not reported	Age 2 to 3 yrs Male: 1.4 Female: 1.2 Age 4 to 5 yrs Male: 1.3 Female: 0.9 Age 6 to 7 yrs Male: 1.1 Female: 0.8 Age 8 to 9 yrs Male: 0.9 Female: 0.8 Age 10 to 11 yrs Male: 0.7 Female: 0.6 Age 12 to 13 yrs Male: 0.9 Female: 0.8 Age 14 to 15 yrs Male: 1.0 Female: 1.1 Age 16 to 17 yrs Male: 1.4 Female: 1.6 If overt reflux ceased, what was the reported age of cessation Not reported	
Full citation Hegar,B., Satari,D.H., Sjarif,D.R.,	**Sample size** n=131	**Details** Study setting Posyandu (a service station for	**Results** The median or mean average age (plus range or	**Limitations** - Presentation of results not particularly clear: for the above

Study details	Participants	Methods	Outcomes and results	Comments
Vandenplas,Y., Regurgitation and gastroesophageal reflux disease in six to nine months old indonesian infants, Pediatric Gastroenterology Hepatology and Nutrition, 16, 240-247, 2013 **Ref Id** 306376 **Country/ies where the study was carried out** Indonesia **Study type** Prospective cohort **Aim of the study** To study the natural history of regurgitation and risk to develop GERD in Indonesian infants older than 6 months presenting with regurgitation using the I-GERQ score, the frequency of regurgitation, weight gain and feeding problems during a period of 3 months follow-up. **Study dates** September 2012 - February 2013 **Source of funding** Not reported	Sample size calculation was done based on the formula for single proportion, using the following parameters: estimated prevalence of GERD in the selected group of infants included in the study is 50%, variation of this prevalence around 10% with a confidence interval at 95%. The minimal sample size was calculated at 97 subjects. Anticipation of loss to follow up was estimated at 30%. Therefore, 130 infants were needed, 131 were included. **Characteristics** Gender, boy/girl, n (%) 80/51 (61.1/38.9) Birth weight in grams, n (range) 3,091 (+448.5) Age at inclusion in months, n (%) 6: 67 (51.1) 7: 27 (20.6) 8: 23 (17.6) 9: 14 (10.7) GER symptoms in family, yes/no, n (%) 59/72 (45/55) **Inclusion Criteria** - Infants aged 6 to 9 months old who regurgitated since more than 2 weeks at least 1 time/day, 4 days/week	healthy children below 5 years, supervised by Primary Health Care Centre) Regurgitation definition used in study The passage of refluxed contents into the pharynx, mouth or from the mouth and inversely related to age Method of obtaining data on regurgitation I-GERQ: consisting of 11 questions including frequency and volume of regurgitation, distress during regurgitation, feeding refusal, weight gain, crying or fussiness, hiccups, arching back, apnea or cyanosis. A score >7 was considered as suggestive for GERD. Sample size calculation See sample size section Sampling Not reported	SD) at which overt reflux was first reported Not reported The median or mean average age (plus range or SD) age at which overt reflux was most frequent Not reported The reported maximum daily frequency of reflux (number of episodes of regurgitation) *Reported as number of infants (%) regurgitating an estimated volume **1-2 times/day** Enrolment 2.5 to 5ml: 77 (58.8) 5 to 15ml: 30 (22.9) 15 to 30ml: 4 (3.1) Total number of infants regurgitating at enrolment (%): 111** (87***) 1st month follow up 2.5 to 5ml: 51 (78.5) 5 to 15ml: 5 (7.7) 15 to 30ml: 3 (4.6) Total number of infants regurgitating at 1st month follow up: 59** (46***) 2nd month follow up 2.5 to 5ml: 40 (88.9) 5 to 15ml: 2 (4.5) 15 to 30ml: 1 (2.2) Total number of infants regurgitating at 2nd month follow up: 43** (34***)	extracted results, it has been assumed that the remaining infants did not regurgitate rather than being considered as missing data (as authors state 4 subjects were lost to follow up) - Unclear how many subjects could have missing data or changed categories in terms of volume of regurgitation - Unclear how many subjects were given conservative treatment **Other information** - If the I-GERQ score was >7, the child was referred to the Hospital for further investigation - If the I-GERQ score was ≤7, the child was seen again the next month, and this during 3 consecutive months - In patients with frequent feeding (>8 times/day) or if the ingested volume was estimated excessive, parental education consisted of avoiding excessive feeding volumes and reducing increased frequency of feeding to normal for the age of the infant - Advice was given to adapt the position of the baby during and after feeding, by holding the baby in vertical position for 30-45 minutes

Study details	Participants	Methods	Outcomes and results	Comments
	Exclusion Criteria - Infants with a clinical suspicion of cow milk allergy - Infants diagnosed with tuberculosis, neurologic disorders such as spasticity, hypotonicity and cerebral palsy - Severely wasted infants (<3SD of the weight to length z score of the WHO 2006 growth chart) - History of gastrointestinal surgery - History of H2 receptor antagonist or proton pump inhibitor treatment		3rd month follow up 2.5 to 5ml: 20 (90.9) 5 to 15ml: 2 (9.1) 15 to 30ml: 0 (0) Total number of infants regurgitating at 3rd month follow up: 22** (17***) **3 to 5 times/day** Enrolment 2.5 to 5ml: 7 (5.3) 5 to 15 ml: 8 (6.1) 15 to 30ml: 3 (2.3) Total number of infants regurgitating at enrolment: 18** (14***) 1st month follow up 2.5 to 5ml: 4 (6.2) 5 to 15ml: 1 (1.5) 15 to 30ml: 1 (1.5) Total number of infants regurgitating at 1st month follow up: 6** (5***) 2nd month follow up 2.5 to 5ml: 1 (2.2) 5 to 15ml: 1 (2.2) 15 to 30ml: 0 (0) Total number of infants regurgitating at 2nd month follow up: 2** (2***) **>5 times/day** Enrolment 2.5 to 5ml: 2 (1.5) 5 to 15ml: 0 (0) 15 to 30ml: 0 (0) Total number of infants regurgitating at enrolment: 2** (2***)	

Study details	Participants	Methods	Outcomes and results	Comments
			Calculated by NCC-WCH based on data reported in the article *%s calculated by NCC-WCH assuming denominator is 127 as 4 subjects were lost to follow up The mean frequency (SD) of regurgitation per day with increasing age Not reported If overt reflux ceased, what was the reported age of cessation Not reported	
Full citation Campanozzi,A., Boccia,G., Pensabene,L., Panetta,F., Marseglia,A., Strisciuglio,P., Barbera,C., Magazzu,G., Pettoello-Mantovani,M., Staiano,A., Prevalence and natural history of gastroesophageal reflux: pediatric prospective survey, Pediatrics, 123, 779-783, 2009 **Ref Id** 238208 **Country/ies where the study was carried out** Italy **Study type** Prospective cohort study	**Sample size** n = 2642, 313 diagnosed with regurgitation, 210 available at follow-up **Characteristics** Age at time of entry to study in months Mean (SD): 5.6 (3.6) Ethnicity, % Not reported Prematurity, % Born premature: not reported Premature at entry to the study: 8.6 Comorbidity, % 0 Type of milk fed Not reported	**Details** Study setting Infants seen in paediatrician offices from north-central and southern Italy Regurgitation definition used in study Rome II criteria - regurgitation ≥ 2 times per day for ≥ 3 weeks plus: - there is no retching, hematemesis, aspiration, apnea, failure to thrive, or abnormal posturing - infant must be 1 to 12 months of age and otherwise healthy - there is no evidence of metabolic, gastrointestinal or CNS disease to explain the symptom Method of obtaining data on regurgitation Each paediatrician was asked to	**Results** The mean age (SD) at which overt reflux was first reported* *Reported as mean age of affected infants 3.8 ± 2.7 months The median or mean average age (plus range or SD) age at which overt reflux was most frequent Not reported The reported maximum daily frequency of reflux (number of episodes of regurgitation) Not reported The mean frequency (SD) of regurgitation per day with increasing age	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Unclear, not reported 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - N/A 1.4 The outcome of interest is adequately measured in study

Study details	Participants	Methods	Outcomes and results	Comments
Aim of the study To evaluate the prevalence and natural history of infant regurgitation in Italian children during the first 2 years of life **Study dates** From April 1 2004 to June 30 2004, each participating paediatrician was asked to record the number of infants examined per day **Source of funding** Not reported	<u>Age at which weaning to solid foods was introduced</u> Not reported **Inclusion Criteria** - Infants seen in the paediatrician's office for acute, chronic care or routine follow-up examination **Exclusion Criteria** - Evidence of metabolic, gastrointestinal or central nervous system diseases - Chronic debilitating diseases - Neurologic abnormalities - Previous surgery of the gastrointestinal tract - Use of acid-suppressive therapy (H2 antagonists, proton-pump inhibitors) - Infants with hematemesis, anaemia, aspiration, apnea, failure to thrive, abnormal posturing, feeding or swallowing difficulties	complete the Infant Gastroesophageal Reflux Questionnaire (I-GERQ) modified at enrolment and during f/up visits, to assess infant regurgitation according to the Rome II criteria. Each child with a diagnosis of regurgitation was re-examined by the same paediatrician with an interval of 2 months until the age of 24 months. <u>Length of follow up (if relevant to study design)</u> 2 years. Follow-up was performed at 6, 12, 18, and 24 months of age. <u>Sample size calculation</u> Not reported <u>Sampling method</u> 75 paediatricians were selected from communities of all sizes, throughout the territory, by random selection of evenly numbered members provided from the membership list of the regional paediatric society.	Not reported <u>If overt reflux ceased, what was the reported age of cessation*</u> *Reported as the number (%) of infants in which regurgitation disappeared Of the 210 subjects followed for 24 months, regurgitation disappeared: By the first 6 months of age in 56 (27%) infants By the first 12 months of age in 128 (61%) infants By the first 18 months of age in 23 (11%) infants At 24 months of age in 3 (1%) infants (Therefore, regurgitation disappeared in all 210 infants by 24 months of age)	participants, sufficient to limit potential bias - Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - N/A 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes **Other information**
Full citation De,S., Rajeshwari,K., Kalra,K.K., Gondal,R., Malhotra,V., Mittal,S.K., Gastrooesophageal reflux in infants	**Sample size** n = 602	**Details** <u>Study setting</u> Subjects were recruited from the well-baby and high risk clinics (consisting of hospital delivered	**Results** <u>The median or mean average age (plus range or SD) at which overt reflux was first reported</u>	**Limitations** <u>NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies</u> 1.1 The study sample

Study details	Participants	Methods	Outcomes and results	Comments
and children in north India, Tropical Gastroenterology, 22, 99-102, 2001 **Ref Id** 238370 **Country/ies where the study was carried out** India **Study type** Cross-sectional study **Aim of the study** To assess the prevalence of gastroesophageal reflux disease as suggested by the symptom profile in babies ranging in age from 1 month to 2 years **Study dates** Not reported **Source of funding** Not reported	**Characteristics** Age at time of entry to study in months, range 1 to 24 Ethnicity, % Not reported Prematurity, % Not reported Comorbidity, % Not reported Type of milk fed Not reported Age at which weaning to solid foods was introduced Not reported **Inclusion Criteria** - Children aged 1 month to 2 years **Exclusion Criteria** - Children who were acutely ill - Children whose date of birth was not known	babies on regular follow-up) and from the outpatient's department (subjects selected from the outpatient's department were those with minor ailments such as common cold). 317 subjects were recruited from the well-baby clinic, 98 from the infant high risk clinic and the remaining from the outpatient's department. Regurgitation definition used in study Not reported Method of obtaining data on regurgitation I-GERQ questionnaire Length of follow up (if relevant to study design) n/a Sample size calculation Not reported Sampling method Not reported	Not reported The median or mean average age (plus range or SD) age at which overt reflux was most frequent Not reported The reported maximum daily frequency of reflux (number of episodes of regurgitation) Not reported The mean frequency (SD) of regurgitation per day with increasing age* *Reported as % with regurgitation at 1 to 6 months, 6 to 12 months and 12 to 24 months 1 to 6 months: 55 6 to 12 months: 15 12 to 24 months: 10 If overt reflux ceased, what was the reported age of cessation Not reported	represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - N/A cross sectional study 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - N/A 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - No, outcome adequately measured but definition of regurgitation used in study is not reported 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - N/A 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes
Full citation Gunasekaran,T.S., Dahlberg,M., Ramesh,P., Namachivayam,G., Prevalence and associated features of gastroesophageal reflux	**Sample size** n= 1286 **Characteristics** Age at time of entry to study in	**Details** Study setting Adolescents from two high schools in suburban areas of Chicago Regurgitation definition used in	**Results** The median or mean average age (plus range or SD) at which overt reflux was first reported Not reported	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of

Study details	Participants	Methods	Outcomes and results	Comments
symptoms in a Caucasian-predominant adolescent school population, Digestive Diseases and Sciences, 53, 2373-2379, 2008 **Ref Id** 237313 **Country/ies where the study was carried out** USA **Study type** Cross-sectional survey **Aim of the study** To determine the prevalence of esophageal-specific GER symptoms and associated respiratory symptoms in a high-school aged population. Also to characterize the percentage of symptomatic adolescent students who took medications for GER symptoms and consulted a physician for these reported symptoms. **Study dates** Questionnaire was distributed to subjects in 2001. **Source of funding** Not reported	<u>years, mean (SD)</u> Mean ± SD: 15.7 ± 1.3 <u>Ethnicity, %</u> Caucasian, 57.3% Asian, 28.4% Hispanic, 6.3% African American, 2.0% Native American, 0.3% Other, 3.8% Not reported, 1.9% <u>Prematurity, %</u> Born premature: Not reported Premature at entry to the study: 0 <u>Comorbidity, %</u> Not reported <u>Type of milk fed</u> Not reported <u>Age at which weaning to solid foods was introduced</u> Not reported **Inclusion Criteria** - Adolescents aged 14-18 years attending two high schools **Exclusion Criteria** Excluded questionnaires that: - did not contain the subject's age - contained answers inconsistent with the questions	<u>study</u> Fluid or food regurgitating to the back of the throat or wet burps <u>Method of obtaining data on regurgitation</u> The adolescent GER questionnaire (ARQ) which was pre-tested by conducting a pilot study. The questionnaire was distributed to students by trained research assistants who explained the contents of the survey, particularly the symptoms. <u>Length of follow up (if relevant to study design)</u> n/a <u>Sample size calculation</u> Not reported <u>Sampling method</u> A sample of students was taken from each of the two high schools. Details not reported.	<u>The median or mean average age (plus range or SD) age at which overt reflux was most frequent</u> Not reported <u>The reported maximum daily frequency of reflux (number of episodes of regurgitation)*</u> *Reported as % of adolescents with no regurgitation, < once/month, once/month, once/week, few times/week and daily No symptoms: 46.1 <once/month: 32.5 once/month: 12.8 once/week: 5.2 few times/week: 2.6 daily: 0.7 <u>The mean frequency (SD) of regurgitation per day with increasing age</u> Not reported <u>If overt reflux ceased, what was the reported age of cessation</u> Not reported	interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - N/A cross sectional study 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - N/A 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - N/A 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes

Study details	Participants	Methods	Outcomes and results	Comments
	- contained no responses to more than two questions			
Full citation Hegar,B., Boediarso,A., Firmansyah,A., Vandenplas,Y., Investigation of regurgitation and other symptoms of gastroesophageal reflux in Indonesian infants, World Journal of Gastroenterology, 10, 1795-1797, 2004 **Ref Id** 238384 **Country/ies where the study was carried out** Indonesia **Study type** Cross-sectional study **Aim of the study** To evaluate the incidence of regurgitation and other symptoms of gastroesophageal reflux in Indonesian infants **Study dates** Not reported **Source of funding** Not reported	**Sample size** n=138 **Characteristics** Age at time of entry to study in months, n (%) 0-3: 74 (53.6) 4-6: 34 (24.6) 7-9: 21 (15.2) 10-12: 9 (6.5) Ethnicity Not reported Prematurity, % Born premature: 0 Premature at entry to the study: 0 Comorbidity, % 0 Type of milk fed Not reported Age at which weaning to solid foods was introduced Not reported **Inclusion Criteria** - Mothers bringing their healthy infants to the Outpatient Clinic for routine immunization (all infants were born at term)	**Details** Study setting Infants attending the Outpatient clinic of the Cipto Mangunkusumo Hospital for routine immunization Regurgitation definition used in study The effortless return of gastric contents into the mouth Method of obtaining data on regurgitation Data was obtained by interviewing mothers using a standard questionnaire about the prevalence of regurgitation during the previous 2 weeks. Name of questionnaire used not reported. Length of follow up (if relevant to study design) n/a Sample size calculation Not reported Sampling method Consecutive mothers	**Results** The median or mean average age (plus range or SD) at which overt reflux was first reported Not reported The median or mean average age (plus range or SD) age at which overt reflux was most frequent Not reported The reported maximum daily frequency of reflux (number of episodes of regurgitation) Not reported The mean frequency (SD) of regurgitation per day with increasing age* *Reported as number of infants (%) with 0 episodes of regurgitation/day, <1 episode of regurgitation/day, 1-4 episodes of regurgitation/day and >4 episodes of regurgitation/day in each age group At 1 month 0 episodes/day: 3 (10) <1 episode/day: 3 (10) 1-4 episodes/day: 18 (55) >4 episodes/day: 8 (25) At 2 months 0 episodes/day: 3 (12)	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - n/a cross sectional study 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - N/A 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - N/A 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes

Study details	Participants	Methods	Outcomes and results	Comments
	Exclusion Criteria Not reported		<1 episode/day: 2 (8) 1-4 episodes/day: 13 (52) >4 episodes/day: 7 (28) At 3 months 0 episodes/day: 5 (29) <1 episode/day: 1 (6) 1-4 episodes/day: 8 (47) >4 episodes/day: 3 (18) At 4 months 0 episodes/day: 6 (60) <1 episode/day: 1 (10) 1-4 episodes/day: 3 (30) >4 episodes/day: 0 (0) At 5 months 0 episodes/day: 3 (21) <1 episode/day: 2 (15) 1-4 episodes/day: 6 (43) >4 episodes/day: 3 (21) At 6 months 0 episodes/day: 6 (60) <1 episode/day: 1 (10) 1-4 episodes/day: 3 (30) >4 episodes/day: 0 (0) At 7 months 0 episodes/day: 6 (60) <1 episode/day: 2 (20) 1-4 episodes/day: 2 (20) >4 episodes/day: 0 (0) At 8 months 0 episodes/day: 1 (33) <1 episode/day: 2 (67) 1-4 episodes/day: 0 (0) >4 episodes/day: 0 (0) At 9 months 0 episodes/day: 8 (100)	**Other information** Other potentially useful data (outcomes not stated in protocol) Number of mothers considering regurgitation as a health problem (by daily regurgitation frequency) <1 episode/day With concern: 3 Without concern: 60 1-4 episodes/day With concern: 24 Without concern: 30 >4 episodes/day With concern: 8 Without concern: 13 Total number of mothers with concern, n (%): 35 (25) Total number of mothers without concern, n (%): 103 (75)

Study details	Participants	Methods	Outcomes and results	Comments
			<1 episode/day: 0 (0) 1-4 episodes/day: 0 (0) >4 episodes/day: 0 (0) At 10 months 0 episodes/day: 4 (80) <1 episode/day: 0 (0) 1-4 episodes/day: 1 (20) >4 episodes/day: 0 (0) At 11 months 0 episodes/day: 1 (100) <1 episode/day: 0 (0) 1-4 episodes/day: 0 (0) >4 episodes/day: 0 (0) At 12 months 0 episodes/day: 2 (67) <1 episode/day: 1 (33) 1-4 episodes/day: 0 (0) >4 episodes/day: 0 (0) If overt reflux ceased, what was the reported age of cessation Not reported	
Full citation Hegar,B., Dewanti,N.R., Kadim,M., Alatas,S., Firmansyah,A., Vandenplas,Y., Natural evolution of regurgitation in healthy infants, Acta Paediatrica, 98, 1189-1193, 2009 **Ref Id** 236808 **Country/ies where the study was carried out**	**Sample size** n = 130 included, 20 subjects dropped out, therefore 110 followed up for 1 year **Characteristics** Age at time of entry to study, mean (SD) Newborns (mean age not reported) Ethnicity, % Not reported	**Details** Study setting Mothers giving birth at the Private Public Hospital at Tangerang, Indonesia Regurgitation definition used in study The effortless return of gastric contents at least into the mouth Method of obtaining data on regurgitation Monthly, data (number of episodes	**Results** The median or mean average age (plus range or SD) at which overt reflux was first reported Not reported The median or mean average age (plus range or SD) age at which overt reflux was most frequent Not reported The reported maximum daily	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the

Study details	Participants	Methods	Outcomes and results	Comments
Indonesia **Study type** Prospective cohort study **Aim of the study** To determine the natural history of infant regurgitation during the first year of life in an unselected population of healthy infants **Study dates** All mothers gave birth during a 3 month period between June and August 2006 **Source of funding** Not reported	Prematurity, % Born premature: 0 Premature at entry to the study: 0 Comorbidity, % 0 Type of milk fed, n(%) Age 0-1 month EBF: 109 (83.8) PBF: 21 (16.2) Age 1-2 months EBF: 98 (75.5) PBF: 32 (24.5) Age 2-3 months EBF: 82 (63.1) PBF: 48 (36.9) Age 3-4 months EBF: 54 (41.9) PBF: 70 (54.3) FM: 5 (3.8) Age 4-5 months EBF: 36 (28.8) PBF: 79 (63.2) FM: 10 (8) Age 5-6 months EBF: 34 (28.1) PBF: 38 (31.4) + SOLID: 49 (40.5) Age 6-7 months Mix feeding: 117 (100) Age 7-8 months Mix feeding: 113 (100) Age 8-9 months	of regurgitation/day) were collected by the mother for 1 week in a diary Length of follow up (if relevant to study design) 1 year. Follow-up consultation was every month during the first 6 months, and every 2 months during the next 6 months, except for an ongoing monthly follow-up of those infants that showed frequent regurgitation >4 times/day at the age of 6 months. Sample size calculation Not reported Sampling method Of all mothers giving birth during a 3 month period, those that could be approached while still in hospital were invited to participate	frequency of reflux (number of episodes of regurgitation) Not reported The mean frequency (SD) of regurgitation per day with increasing age* *Reported as n (%) of infants with regurgitation with increasing age Age 0-1 month No regurgitation: 25 (19.2) <1 episode/day: 10 (7.7) 1-4 episodes/day: 69 (53.1) >4 episodes/day: 26 (20) Age 1-2 months No regurgitation: 23 (17.7) <1 episode/day: 12 (9.3) 1-4 episodes/day: 70 (53.8) >4 episodes/day: 25 (19.2) Age 2-3 months No regurgitation: 28 (21.5) <1 episode/day: 14 (10.8) 1-4 episodes/day: 67 (51.5) >4 episodes/day: 21 (16.2) Age 3-4 months No regurgitation: 35 (27.1) <1 episode/day: 15 (12.0) 1-4 episodes/day: 64 (49.6) >4 episodes/day: 15 (12.0) Age 4-5 months No regurgitation: 47 (37.6) <1 episode/day: 16 (12.8) 1-4 episodes/day: 52 (41.6) >4 episodes/day: 10 (8.0) Age 5-6 months	sample), sufficient to limit potential bias - No, all dropouts because of excessive symptoms were in the partially breastfed group 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - N/A 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - N/A 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes

Study details	Participants	Methods	Outcomes and results	Comments
	Mix feeding: 110 (100) Age 9-10 months Mix feeding: 110 (100) Age 10-11 months Mix feeding: 110 (100) Age 11-12 months: Mix feeding: 110 (100) Age 12-13 months Mix feeding: 110 (100) *EBF: exclusively breastfed, PBF: partially breastfed, FM: formula milk <u>Age at which weaning to solid foods was introduced</u> After 5 months **Inclusion Criteria** - Infants had to be term-born - Absence of congenital abnormalities or apparent disease - Mothers needed to have at least a high school education level **Exclusion Criteria** - Parents who refused to sign the informed consent - Families living outside the hospital area and that had no possibility to come to the follow-up consultations		No regurgitation: 60 (49.6) <1 episode/day: 10 (8.3) 1-4 episodes/day: 45 (37.2) >4 episodes/day: 6 (5.0) <u>Age 6-7 months</u> No regurgitation: 71 (60.7) <1 episode/day: 13 (11.1) 1-4 episodes/day: 30 (25.6) >4 episodes/day: 3 (2.6) <u>Age 7-8 months</u> No regurgitation: 79 (69.9) <1 episode/day: 10 (8.9) 1-4 episodes/day: 23 (20.3) >4 episodes/day: 1 (0.9) <u>Age 8-9 months</u> No regurgitation: 82 (74.5) <1 episode/day: 5 (4.6) 1-4 episodes/day: 23 (20.9) >4 episodes/day: 0 (0.0) <u>Age 9-10 months</u> No regurgitation: 85 (77.3) <1 episode/day: 5 (4.5) 1-4 episodes/day: 20 (18.2) >4 episodes/day: 0 (0.0) <u>Age 10-11 months</u> No regurgitation: 91 (82.7) <1 episode/day: 2 (1.8) 1-4 episodes/day: 17 (15.5) >4 episodes/day: 0 (0.0) <u>Age 11-12 months</u> No regurgitation: 96 (87.3) <1 episode/day: 5 (4.5) 1-4 episodes/day: 9 (8.2) >4 episodes/day: 0 (0.0) <u>Age 12-13 months</u>	

Study details	Participants	Methods	Outcomes and results	Comments
	- Regular vomiting		No regurgitation: 102 (92.8) <1 episode/day: 4 (3.6) 1-4 episodes/day: 4 (3.6) >4 episodes/day: 0 (0.0) If overt reflux ceased, what was the reported age of cessation Not reported	
Full citation Iacono,G., Merolla,R., D'Amico,D., Bonci,E., Cavataio,F., Di,Prima L., Scalici,C., Indinnimeo,L., Averna,M.R., Carroccio,A., Paediatric Study Group on Gastrointestinal Symptoms in Infancy., Gastrointestinal symptoms in infancy: a population-based prospective study, Digestive and Liver Disease, 37, 432-438, 2005 **Ref Id** 237281 **Country/ies where the study was carried out** Italy **Study type** Prospective cohort **Aim of the study** To ascertain the frequency of the most common gastrointestinal symptoms in infants during the first 6 months after birth and to evaluate	**Sample size** n= 3000 included, 2879 at follow-up **Characteristics** Age at time of entry to study in days, mean (SD) 10.1 ± 2.2 Ethnicity, % Not reported Prematurity, % Born premature: not reported Premature at entry to the study: not reported Comorbidity,% 0 Type of milk fed, n (%)* Breast-fed: 2332 (81) Mixed-fed: 230 (8) Bottle-fed: 317 (11) *The reported %'s are at time of entry to the study. During the study period, many infants changed their feeding habits, with a progressive reduction in exclusively breast-fed and an increase in mixed- or bottle-	**Details** Study setting Infants registered with paediatricians distributed throughout Italy (40 in the north of Italy, 35 in the centre, 40 in the south and 25 in the islands) Regurgitation definition used in study Regurgitation was defined as the loss of a small part of the meal, without retching Method of obtaining data on regurgitation Paediatricians were asked to record the presence of gastrointestinal symptoms in the first 20 infants to be registered with them during the study period. Data were collected using a standard clinical chart. Symptoms were recorded whenever the parents requested a clinical check-up or during a set monthly visit. Length of follow up (if relevant to study design) 6 months	**Results** The median or mean average age (plus range or SD) at which overt reflux was first reported* *Reported as mean age of diagnosis Regurgitation: 32 ± 25 days Vomiting: 43 ± 30 days The median or mean average age (plus range or SD) age at which overt reflux was most frequent Not reported The reported maximum daily frequency of reflux (number of episodes of regurgitation) Not reported The mean frequency (SD) of regurgitation per day with increasing age Not reported If overt reflux ceased, what was the reported age of cessation Not reported	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Yes 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - N/A 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - N/A 1.6 The statistical analysis is

Study details	Participants	Methods	Outcomes and results	Comments
the influence of some variables on the onset of the symptoms **Study dates** Study was carried out between January and December 1999 **Source of funding** Not reported	fed subjects Age at which weaning to solid foods was introduced Not reported **Inclusion Criteria** - Age at entry to the study of less than 2 weeks - Absence of any disease diagnosed before entry to the study **Exclusion Criteria** - Infants older than 2 weeks - Infants with a definite diagnosis of gastroenterological, respiratory, urinary, neurological or metabolic disease	Sample size calculation Not reported Sampling method Not reported		appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes
Full citation Martin,A.J., Pratt,N., Kennedy,J.D., Ryan,P., Ruffin,R.E., Miles,H., Marley,J., Natural history and familial relationships of infant spilling to 9 years of age, Pediatrics, 109, 1061-1067, 2002 **Ref Id** 238200 **Country/ies where the study was carried out** Australia	**Sample size** n= 1981 at birth, 836 at 24 month follow-up **Characteristics** Age at time of entry to study in months, mean (SD) Newborns (mean not reported) Ethnicity, % Not reported Prematurity, % Born premature: Not reported Premature at entry to the study: Not	**Details** Study setting Infants born at the Queen Victoria Hospital, Adelaide (the major teaching maternity hospital) Regurgitation definition used in study Spilling was defined as equivalent to regurgitation and/or vomiting of most feeds (50% or more) on a daily basis i.e. where feeds or gastric contents are returned and are visible emanating from the mouth either in large or small quantity	**Results** The median or mean average age (plus range or SD) at which overt reflux was first reported Not reported The median or mean average age (plus range or SD) age at which overt reflux was most frequent Not reported The reported maximum daily frequency of reflux (number of episodes of regurgitation) Not reported	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Unclear 1.3 The prognostic factor of

Study details	Participants	Methods	Outcomes and results	Comments
Study type Prospective cohort study **Aim of the study** To determine the natural history of infant spilling (regurgitation/vomiting) during the first 2 years of life and to determine the relationship between infant spilling and gastroesophageal reflux symptoms at 9 years of age **Study dates** Mothers of infants born between May 1987 and April 1988 were approached **Source of funding** Supported by the Australian National Health and Medical Research Council grant	reported <u>Comorbidity, %</u> Not reported <u>Type of milk fed, % breastfed</u> At hospital discharge: 89 At 4 months of age: 70 At 12 months of age: 25 <u>Age at which weaning to solid foods was introduced</u> Not reported **Inclusion Criteria** - Mothers of infants born at the Queen Victoria Hospital, Adelaide between May 1987 and April 1988 **Exclusion Criteria** - Mothers who could not read English - Mothers who lived outside Adelaide and were not available by telephone - Mothers whose infants were dying or to be adopted	<u>Method of obtaining data on regurgitation</u> Parents were asked to keep daily symptom diaries for the first 2 years of life. Diaries were a monthly card displayed prominently in the kitchen and checked daily. <u>Length of follow up (if relevant to study design)</u> From birth to 2 years of life then reviewed at 9 years of age <u>Sample size calculation</u> Not reported <u>Sampling method</u> Not reported	<u>The mean frequency (SD) of regurgitation per day with increasing age*</u> *Reported as % of infants with spilling at different ages 3 to 4 months: 41 13 to 14 months: <5 19 months: negligible <u>If overt reflux ceased, what was the reported age of cessation</u> 19 months	interest is adequately measured in study participants, sufficient to limit potential bias - N/A 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - N/A 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes
Full citation Miyazawa,R., Tomomasa,T., Kaneko,H., Tachibana,A., Ogawa,T., Morikawa,A., Prevalence of gastro-esophageal reflux-related symptoms in Japanese infants, Pediatrics International, 44, 513-516, 2002	**Sample size** n = 921 **Characteristics** <u>Age at time of entry to study in months, n/N (%)</u>	**Details** <u>Study setting</u> Three public health centers at the Gunma prefecture - monthly healthy baby check-ups in Kasagake town, Hara town and Tone city.	**Results** <u>The median or mean average age (plus range or SD) at which overt reflux was first reported</u> Not reported <u>The median or mean</u>	**Limitations** <u>NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies</u> 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit

Study details	Participants	Methods	Outcomes and results	Comments
Ref Id 238218 **Country/ies where the study was carried out** Japan **Study type** Cross-sectional study **Aim of the study** To determine the natural course of GER in Japanese children, including the prevalence of regurgitation or vomiting and other GER-related symptoms and complications in infants visiting for healthy baby check-ups **Study dates** Survey conducted between August 2000 to August 2001 **Source of funding** Not reported	1 month: 157/921 (17) 4 months: 458/921 (50) 7 months: 156/921 (17) 12 months: 150/921 (16) Ethnicity, % Not reported Prematurity, % Born premature: 0 Premature at entry to the study: 0 Comorbidity, % 0 Type of milk fed Not reported for all subjects Age at which weaning to solid foods was introduced Not reported **Inclusion Criteria** - Mothers of infants who visited for healthy baby check-ups at 1,4,7 and 12 months after birth **Exclusion Criteria** - Infants who were born prematurely (less than 35 weeks' gestation) - Infants with a chronic medical or developmental problem - Infants who had been ill in the past 2 weeks	Regurgitation definition used in study The effortless return of small volumes of gastric contents into the pharynx and mouth Method of obtaining data on regurgitation Questionnaires were distributed to the mothers of infants and answers were checked by one pediatrician who was conducting routine check-ups. If infants had regurgitation or vomiting once or more a day, further questions were asked by another physician. (Name of questionnaire used not reported) Length of follow up (if relevant to study design) Sample size calculation Not reported Sampling method Not reported	average age (plus range or SD) age at which overt reflux was most frequent Not reported The reported maximum daily frequency of reflux (number of episodes of regurgitation) Not reported The mean frequency (SD) of regurgitation per day with increasing age* *Reported as % of infants with different frequencies of regurgitation or vomiting per day with increasing age 1 month One or more episode/day: 47.1 Three or more episodes/day: 14.0 4 months One or more episode/day: 28.8 Three or more episodes/day: 11.4 7 months One or more episode/day: 6.4 Three or more episodes/day: 2.6 12 months One or more episode/day: 0.0 Three or more episodes/day: 0.0	potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - N/A 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - N/A 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - N/A 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes **Other information** * Data in graph format without the corresponding %'s reported has not be extracted

Study details	Participants	Methods	Outcomes and results	Comments
			If overt reflux ceased, what was the reported age of cessation Not reported	
Full citation Nelson,S.P., Chen,E.H., Syniar,G.M., Christoffel,K.K., One-year follow-up of symptoms of gastroesophageal reflux during infancy. Pediatric Practice Research Group, Pediatrics, 102, E67-, 1998 **Ref Id** 216389 **Country/ies where the study was carried out** USA **Study type** Case-control study **Aim of the study** To determine what percentage of infants outgrow regurgitation over 1 year, determine whether they develop feeding or mealtime problems and whether they develop frequent respiratory illnesses, including ear, sinus, and upper respiratory infections, or wheezing episodes. **Study dates**	**Sample size** Cases: n= 63 Controls: n= 92 **Characteristics** Age at time of entry to study in months, mean (range) Cases: 7.2 (6-12) Controls: 8.2 (6-12) Ethnicity, % white Cases: 97 Controls: 92 Prematurity, % Born premature: Not reported Premature at entry to the study: 0 Comorbidity, % 0 Type of milk fed Not reported Age at which weaning to solid foods was introduced Not reported **Inclusion Criteria** - Parents of healthy infants 6 to 12 months old (Cases*: with	**Details** Study setting Infants attending 12 different (urban, suburban and rural) practices in the Pediatric Practice Research Group in the Chicago area Regurgitation definition used in study Not reported Method of obtaining data on regurgitation Parents completed two surveys concerning their child 1) The Infant Gastroesophageal Reflux Questionnaire-Shortened and Revised Form (IGER-SF) and the Children's Eating Behavior Inventory (CEBI) Length of follow up (if relevant to study design) 1 year Sample size calculation Not reported Sampling method Not reported	**Results** The median or mean average age (plus range or SD) at which overt reflux was first reported Not reported The median or mean average age (plus range or SD) age at which overt reflux was most frequent Not reported The reported maximum daily frequency of reflux (number of episodes of regurgitation)* *Reported as % of infants spitting up ≥ 1 time/day Cases Initial: 94 1-year follow-up: 0 Controls Initial: 0 1-year follow-up: 0 The mean frequency (SD) of regurgitation per day with increasing age Not reported If overt reflux ceased, what was the reported age of cessation	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Unclear - reasons for lost to follow-up not reported 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - N/A 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - No, regurgitation definition used in study not reported 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - N/A 1.6 The statistical analysis is appropriate for the design of the

Study details	Participants	Methods	Outcomes and results	Comments
Follow-up surveys were mailed to parents from June to September 1996. **Source of funding** Not reported	regurgitation, Controls**: no regurgitation) * Cases were identified by parents who described spitting up was a problem for their child (28%) or reported that their child spit up one or more times a day (10%) ** Controls were matched to cases by age and practice strata **Exclusion Criteria** Not reported		Not reported	study, limiting potential for the presentation of invalid results - Yes **Other information** Other potentially useful data (outcomes not stated in protocol) % of parents reporting spitting up was a problem Cases Initial: 38 1-year follow-up: 0 Controls Initial: 0 1-year follow-up: 0
Full citation Nelson,S.P., Chen,E.H., Syniar,G.M., Christoffel,K.K., Prevalence of symptoms of gastroesophageal reflux during infancy. A pediatric practice-based survey. Pediatric Practice Research Group, Archives of Pediatrics and Adolescent Medicine, 151, 569-572, 1997 **Ref Id** 237049 **Country/ies where the study was carried out** USA	**Sample size** n = 948 **Characteristics** Age at time of entry to study in months, mean (SD) 4.5 ± 3.8 Ethnicity, % Non-Hispanic white: 100 (Other ethnic subsamples were too small to be included in this analysis) Prematurity, % Born premature: 0 Premature at entry to the study: 0 Comorbidity, %	**Details** Study setting 19 Pediatric Practice Research Group practices in the Chicago, Ill, area (urban, suburban and semirural offices) Regurgitation definition used in study Not reported Method of obtaining data on regurgitation The Infant Gastroesophageal Reflux Questionnaire - Shortened and Revised Form (IGER-SF) were distributed to caregivers of infants younger than 13 months in 19 practices. In 7 practices, surveys were distributed by office personnel	**Results** The median or mean average age (plus range or SD) at which overt reflux was first reported Not reported The median or mean average age (plus range or SD) age at which overt reflux was most frequent Not reported The reported maximum daily frequency of reflux (number of episodes of regurgitation) Not reported The mean frequency (SD) of regurgitation per day with	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - N/A cross sectional study 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient

Study details	Participants	Methods	Outcomes and results	Comments
Study type Cross-sectional survey **Aim of the study** To determine the prevalence of symptoms associated with overt gastroesophageal reflux during the first year of life, to describe when most infants outgrow these symptoms and to assess the prevalence of parental reports of various symptoms associated with GER and the percentages of infants who have been treated for GER **Study dates** Questionnaires were distributed to caregivers of infants from June to August 1995 **Source of funding** Not reported	0 Type of milk fed Not reported Age at which weaning to solid foods was introduced Not reported **Inclusion Criteria** - Caregivers of healthy infants younger than 13 months in 19 practices in the Pediatric Practice Research Group **Exclusion Criteria** Caregivers of infants: - who were born prematurely (<37 weeks' gestation) - with a chronic medical or developmental problem - who had been ill in the past 2 weeks All repeat responders were also excluded	trained by one of the study authors and given only to caregivers of infants who were there for a well-child visit. Trained research assistants distributed the survey in the other 12 practices to all parents of infants in the office. Surveys were available in both English and Spanish. Length of follow up (if relevant to study design) n/a Sample size calculation Not reported Sampling method No details regarding how the 19 practices were selected is given. Daily appointment schedules or sign-in logs from each participating practice were reviewed. Caregivers of 82% of age-eligible infants completed the questionnaire.	increasing age* *Reported as % with regurgitation with increasing age At least 1 episode per day 0 to 3 month olds: 50 4 months: 67 6 months: 61 7 months: 21 10 to 12 month olds: 5 At least 4 episodes per day 5 months: 23 7 months: 7 If overt reflux ceased, what was the reported age of cessation Not reported	to limit potential bias - N/A 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - No, outcome adequately measured but definition of regurgitation used in study is not reported 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - N/A 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes **Other information** * Data in graph format without the corresponding %'s reported has not be extracted Other potentially useful data (outcomes not stated in protocol) % of parents reporting regurgitation as a problem 0 to 3 months: 14 6 months: 23 7 months: 14 10 to 12 months: 3.2
Full citation	**Sample size** Normal babies	**Details** Study setting	**Results** The mean age (SD) at which	**Limitations** NICE guidelines manual 2012:

Study details	Participants	Methods	Outcomes and results	Comments
Orenstein,S.R., Shalaby,T.M., Cohn,J.F., Reflux symptoms in 100 normal infants: diagnostic validity of the infant gastroesophageal reflux questionnaire, Clinical Pediatrics, 35, 607-614, 1996 **Ref Id** 219933 **Country/ies where the study was carried out** USA **Study type** Case-control study **Aim of the study** To identify the prevalence of reflux symptoms in normal infants, to characterize the I-GERQ's diagnostic validity for separating nonreferred normal infants from referred infants who have positive diagnostic tests (esophageal biopsy or pH probe), and to identify potentially provocative caretaking practices. **Study dates** - 'Normal' infants were recruited from those attending the well-baby clinic between January 17 and November 20, 1992 - 'GORD' babies were those referred	n=100 GORD babies n=35 **Characteristics** Age at time of entry to study in weeks, median (range) Normal babies: 19 (3 to 60) GORD babies: 15 (4 to 56) Ethnicity, % Not reported Prematurity, % Normal babies Born premature: not reported Premature at entry to the study: 26 GORD babies Born premature: not reported Premature at entry to the study: 14 Comorbidity, % 0 Type of milk fed, % breastfed ever Normal babies: 27 GORD babies: 26 Age at which weaning to solid foods was introduced Not reported **Inclusion Criteria** Normal babies - Consecutive infants younger than 14 months of age attending the well-baby clinic	Well-baby clinic of Children's Hospital of Pittsburgh Regurgitation definition used in study Not reported Method of obtaining data on regurgitation The I-GERQ questionnaire was completed by a parent of each infant, reading and marking it without assistance Length of follow up (if relevant to study design) n/a Sample size calculation Not reported Sampling method Consecutive sampling	overt reflux was first reported Not reported The median or mean average age (plus range or SD) age at which overt reflux was most frequent Not reported The reported maximum daily frequency of reflux (number of episodes of regurgitation)* *Reported as % of infants with regurgitation >once/day, >3 times/day and > 5 times/day Normal babies >once/day: 40 >3 times/day: 15 >5 times/day: 6 GORD babies >once/day: 80 >3 times/day: 51 >5 times/day: 31 The mean frequency (SD) of regurgitation per day with increasing age Not reported If overt reflux ceased, what was the reported age of cessation Not reported	Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - N/A 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - N/A 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - No, definition of regurgitation used in study not reported 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - N/A 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes

Study details	Participants	Methods	Outcomes and results	Comments
for evaluation between April 1 1989 and September 30 1991 **Source of funding** Supported in part by grants from the National Institute of Health and by United States Public Health Service grant	GORD babies - Infants younger than 14 months of age referred to the gastroenterology division for evaluation for GERD and tested positive on either 24-hour pH probe (pH<4 for> 10% of the total time) or esophageal suction biopsy (basal layer >25% or papillary height >50%) **Exclusion Criteria** Normal babies - Prior reflux evaluation (pH probe, upper gastrointestinal radiography, esophageal biopsy) or treatment (antacid agent, prokinetic agent) GORD babies - Not reported			
Full citation Osatakul,S., Sriplung,H., Puetpaiboon,A., Junjana,C.O., Chamnongpakdi,S., Prevalence and natural course of gastroesophageal reflux symptoms: a 1-year cohort study in Thai infants, Journal of Pediatric Gastroenterology and Nutrition, 34, 63-67, 2002 **Ref Id** 237834 **Country/ies where the study was**	**Sample size** n=216 enrolled, 145 at follow-up **Characteristics** Age at time of entry to study in months, mean (SD) Newborns aged 1 month (mean (SD) not reported) Ethnicity, % Not reported Prematurity, % Born premature: 0	**Details** Study setting Neonates were recruited from the well-baby clinic of Songklanagarind Hospital Regurgitation definition used in study Not clearly defined. An infant who regurgitated at least 1 day per week was considered to have reflux regurgitation. During the follow-up period, infants with reflux regurgitations were considered to be free of symptoms when their regurgitation did not occur, as	**Results** The median or mean average age (plus range or SD) at which overt reflux was first reported Not reported The median or mean average age (plus range or SD) age at which overt reflux was most frequent Not reported The reported maximum daily frequency of reflux (number of episodes of regurgitation)	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Yes

Study details	Participants	Methods	Outcomes and results	Comments
carried out Thailand **Study type** Prospective cohort **Aim of the study** To investigate the prevalence of symptoms related to gastroesophageal reflux in Thai infants and to describe the clinical course of reflux regurgitation during the first year of life **Study dates** Neonates attended the well-baby clinic between March and June 1998 **Source of funding** Supported by a grant from Prince of Songkla University, Thailand	Premature at entry to the study: 0 Comorbidity, % 0 Type of milk fed, % At 1 month: breast fed - 27.6, cow milk formula - 10.3, breast milk combined with cow milk - 62.1 At 2 months: breast fed - 26.2, cow milk formula - 20.7, breast milk combined with cow milk - 53.1 Age at which weaning to solid foods was introduced At 4 months in 90.2% of infants, by 6 months in all infants **Inclusion Criteria** - Healthy newborns aged 1 month who attended the well-baby clinic of a hospital in Southern Thailand **Exclusion Criteria** - Newborns with a history of birth asphyxia, prematurity, congenital anomalies or underlying disease	shown in the diary for at least 4 consecutive weeks. Method of obtaining data on regurgitation The history of reflux symptoms was obtained by interviewing the parents (the same interviewer for all subjects). Diaries were provided to parents/carers for recording the occurrence of regurgitation. Using this diary, objective information about the frequency of regurgitation in infants was obtained. Length of follow up (if relevant to study design) 1 year. All infants were evaluated every 2 months at regular well-baby clinic visits for 1 year. Sample size calculation A sample size of 100 newborns was calculated, based on the 50% prevalence of regurgitation in early infancy from a previous study (P=0.5) with 95% confidence and 10% precision. 200 newborns were enrolled to allow a 50% dropout rate. Sampling method Not reported	Not reported The mean frequency (SD) of regurgitation per day with increasing age At 1 month: 2.3 (1.8) At 2 months: 1.9 (1.2) At 4 months: 1.8 (1.2) At 6 months: 1.4 (0.8) At 8 months: 1.2 (0.4) At 10 months: 1.0 (0.2) At 12 months: 1.3 (0.5) % of infants with 1-3 episodes of regurgitation/day, 4-6 episodes of regurgitation/day, >6 episodes of regurgitation/day in each age group At 1 month 1-3 episodes/day: 85.7 4-6 episodes/day: 9.8 >6 episodes/day: 4.5 At 2 months 1-3 episodes/day: 93.2 4-6 episodes/day: 5.1 >6 episodes/day: 1.7 At 4 months 1-3 episodes/day: 93.8 4-6 episodes/day: 4.2 >6 episodes/day: 2.0 At 6 months 1-3 episodes/day: 96.6 4-6 episodes/day: 3.4 >6 episodes/day: 0 At 8 months	1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - N/A 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - No, definition of regurgitation not reported 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - N/A 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes **Other information** Other potentially useful data (outcomes not stated in protocol) Prevalence, % (95% CI) of regurgitation with increasing age At 1 month: 79.3 (72.6 to 86) At 2 months: 86.9 (81.4 to 92.4) At 4 months: 69.7 (62.3 to 77.1) At 6 months: 45.5 (37.5 to 53.5) At 8 months: 22.8 (16.1 to 29.5) At 10 months: 12.4 (7.1 to

Study details	Participants	Methods	Outcomes and results	Comments
			1-3 episodes/day: 100 4-6 episodes/day: 0 >6 episodes/day: 0 <u>At 10 months</u> 1-3 episodes/day: 100 4-6 episodes/day: 0 >6 episodes/day: 0 <u>At 12 months</u> 1-3 episodes/day: 100 4-6 episodes/day: 0 >6 episodes/day: 0 <u>If overt reflux ceased, what was the reported age of cessation</u> Not reported	17.7) At 12 months: 7.6 (3.3 to 11.9) <u>Prevalence, % of regurgitation with increasing age according to the severity of reflux (severity determined by the number of days of regurgitation per week)</u> <u>At 1 month</u> Regurgitation 1 to 3 days a week: 39.3 Regurgitation 4 to 6 days a week: 6.9 Regurgitation daily: 33.1 <u>At 2 months</u> Regurgitation 1 to 3 days a week: 43.4 Regurgitation 4 to 6 days a week: 25.5 Regurgitation daily: 17.9 <u>At 4 months</u> Regurgitation 1 to 3 days a week: 48.2 Regurgitation 4 to 6 days a week: 13.1 Regurgitation daily: 8.3 <u>At 6 months</u> Regurgitation 1 to 3 days a week: 39.3 Regurgitation 4 to 6 days a week: 4.1 Regurgitation daily: 2.1 <u>At 8 months</u> Regurgitation 1 to 3 days a week: 17.2 Regurgitation 4 to 6 days a week: 4.8 Regurgitation daily: 0.7

Study details	Participants	Methods	Outcomes and results	Comments
				At 10 months Regurgitation 1 to 3 days a week: 12.4 Regurgitation 4 to 6 days a week: 0 Regurgitation daily: 0 At 12 months Regurgitation 1 to 3 days a week: 7.6 Regurgitation 4 to 6 days a week: 0 Regurgitation daily: 0
Full citation Van,HoweR, Storms,M.R., Gastroesophageal reflux symptoms in infants in a rural population: longitudinal data over the first six months, BMC Pediatrics, 10, 7-, 2010 **Ref Id** 237100 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** To prospectively measure reported gastroesophageal reflux symptoms in healthy term infants for the first six	**Sample size** n= 128 **Characteristics** Age at time of entry to study, mean (SD) Newborns, 39.6 (1.1) weeks gestational age Ethnicity, % Caucasian: 95.19 Native American: 2.43 Mixed race: 1.00 African American: 0.86 Hispanic: 0.33 Asian American: 0.19 Prematurity, % Born premature: 0 Premature at entry to the study: 0 Comorbidity, % 0 Type of milk fed	**Details** Study setting Infants delivered at Marquette General Hospital, a rural referral hospital Regurgitation definition used in study Not reported Method of obtaining data on regurgitation The Infant Gastroesophageal Reflux Questionnaire Revised (I-GERQ-R) was completed by mothers at the one-month, two-month, four-month, and six-month well child visits with the infant care provider Length of follow up (if relevant to study design) 6 months Sample size calculation Not reported	**Results** The median or mean average age (plus range or SD) at which overt reflux was first reported Not reported The median or mean average age (plus range or SD) age at which overt reflux was most frequent Not reported The reported maximum daily frequency of reflux (number of episodes of regurgitation) Not reported The mean frequency (SD) of regurgitation per day with increasing age At 1 month: 2.31 (SD: 1.90) At 2 months: 2.19 (SD: 1.89) At 4 months: 2.30 (SD:1.87) At 6 months: 1.46 (SD: 1.53)	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Unclear 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - N/A 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - No - definition of regurgitation not reported 1.5 Important potential

Study details	Participants	Methods	Outcomes and results	Comments
months of life **Study dates** Mother-infant pairs were enrolled from January 23 2006 to October 3 2006 **Source of funding** Supported by a grant from The Gerber Foundation	Not reported <u>Age at which weaning to solid foods was introduced</u> Not reported **Inclusion Criteria** - Mother-infant pairs who delivered at Marquette General Hospital (healthy term infants) **Exclusion Criteria** - Follow-up with physicians not participating in the study (primarily outside of Marquette, Michigan) - Gestational age of less than 36 weeks - Twins - Admission to the neonatal intensive care unit	<u>Sampling method</u> Consecutive sampling of mother-infant pairs who delivered at Marquette General Hospital	<u>If overt reflux ceased, what was the reported age of cessation</u> Not reported	confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - N/A 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes

I.2 How do you distinguish between GOR and GORD?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Ammari,M., Djeddi,D., Leke,A., Delanaud,S., Stephan-Blanchard,E., Bach,V., Telliez,F., Relationship between sleep and acid gastro-oesophageal reflux in neonates, Journal of Sleep Research, 21, 80-86, 2012 **Ref Id** 237941 **Country/ies where the study was carried out** France **Study type** Case-control study **Aim of the study** Analyse the impact of acid GOR on sleep in neonates and, reciprocally, the influence of wakefullness and sleep stages on the characteristics of acid reflux. **Study dates** Not stated	**Sample size** 25 neonates **Characteristics** 25 infants age - 35.8 weeks (SD 4.6) No severe disease GOR group (n = 18) Age 35.1 weeks (5.1) Control group (n = 7) Age 36.2 weeks (4.5) **Inclusion Criteria** Referred for pH monitoring for suspected GORD No medication administered before or during the investigation. **Exclusion Criteria** None stated	**Tests** Multichannel intraluminal impedance pH monitoring to monitor reflux using recommendations of ESPGHAN. Polysomnography to monitor sleep patterns	**Methods** Study design: Case-control study Setting: Paediatric department at university hospital Ethics: Local ethics approval and parental consent obtained. Patient recruitment: Children referred for overnight pH monitoring. Data collection Multichannel intraluminal impedance pH monitoring to monitor reflux. - RI calculated as % time below pH 4.0 - Total number of episodes - Mean duration of episodes - Frequency of episodes Polysomnography to monitor sleep patterns Positive and negative cases of GORD Not specified in detail "presence of GOR" Statistical analysis: Mann-Whitney U test	**Results** Outcome: Control group, GOR group Sleep period (minutes): 740 (SD 117), 683 (SD 171) Total sleep time (minutes): 559 (SD 125), 487 (SD 127) Sleep efficiency (%): 75 (11), 72 (9) Sleep structure: Wakefullness: 24.8 (11.0), 27.0 (10.0) Active sleep: 58.4 (10.0), 63.8 (9.7) Indeterminate sleep: 8.4 (6.9), 7.2 (4.7) Quiet Sleep: 33.1 (7.8), 29.7 (8.6) All comparisons were non-significant at $p < 0.05$	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding Picardy regional council post-doctoral research grant.					Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes, undertaken before survey Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No. however, it is only measure of it. Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No All children were being investigated for GORD, so had symptoms significant enough to require investigation.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Definition of GORD not defined in detail.
Full citation Assadamongkol,K., Phuapradit,P., Petsrikun,K., Viravithya,W., Gastroesophageal reflux in children: correlation of symptoms with 24-hour esophageal pH monitoring, Journal of the Medical Association of Thailand = Chotmaihet thangphaet, 76 Suppl 2, 49-54, 1993 **Ref Id** 237952 **Country/ies where the study was carried out** Thailand **Study type** Prospective cohort study **Aim of the study** The occurence and clinical presentations of the pathological GER using 24-hour oesophageal monitoring and studied the clinical significance of all pathological GER using diagnosic values.	**Sample size** 55 **Characteristics** 35 boys and 20 girls Age range 1 month to 12 years **Inclusion Criteria** Children referred for suspected GER **Exclusion Criteria** None stated	**Tests** <u>GER</u> 18-24 hour pH monitoring	**Methods** Study design: Prospective cohort Setting: Hospital Ethics: Not mentioned Positive and negative cases: Based on criteria outlined by Boix-Ochoa. Not described in detail. Statistical analysis: Sensitivity, specificity, PPV and NPV	**Results** 26 of 55 children had pathological GER <u>Symptom: Sensitivity %, Specificity %, PPV %, NPV %, n with symptoms</u> Frequent vomiting: 7.7, 82.8, 28.6, 50, 7 Dysphagia: 7.7, 100, 100, 54.7, 2 Apnoea: 11.5, 96.6, 75, 54.9, 4 Aspiration pneumonia: 7.7, 96.6, 66.7, 52.8, 3 Hyperreactive airway: 15.4, 96.6, 80, 56, 5 Recurrent pneumonia: 50, 31, 39.4, 39.1, 33 Stridor: 0, 96.6, 0, 51.9, 1	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? Yes, but small sample size Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? Yes, initial selection was based on clinical interpretation. Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? No If a threshold was used, was it pre-specified? Yes, presence of symptom or not Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study dates August 1990 to April 1993 **Source of funding** Not stated					index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes, undertaken before survey Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No. However, it is only measure of it. Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Aydin,E., Tastan,E.,	**Sample size** 20 cases with OME and	**Tests** 24 hour pH monitoring	**Methods** Study design:	**Results** Test results for distal	**Limitations** Quality assessment based

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aydogan,F., Arslan,N., Karaca,G., Role of nasopharyngeal reflux in the etiology of otitis media with effusion, Journal of Otolaryngology - Head and Neck Surgery, 40, 499-503, 2011 **Ref Id** 237717 **Country/ies where the study was carried out** Turkey **Study type** Case-control study **Aim of the study** Investiagate Nasopharyngeal reflux in children with Otitis Media with Effusion **Study dates** February 2010 to July 2010 **Source of funding** Not stated	adenoid hypertrophy 20 controls with adenoid hypertrophy only **Characteristics** Cases: 12 females and 8 males Average age 7.7 years (range 4 to 13 years) Controls: 11 females and 9 males Average age 7.2 yeats (range 3 to 12 years) **Inclusion Criteria** Children with adenoid hypertrophy with or without tonsillar hypertrophy Cases where children with OME **Exclusion Criteria** History of allergic rhinitis, immune deficiency or metabolic disease	Diagnosis of GERD based on DeMeester scoring system: Number of reflux episodes: 50 % time pH < 4: 4.2 Number of episodes lasting longer than 5 minutes: 4.0 Duration of longest episode: 9.2 OME varified by Otomicroscopic examination and tympanometry	Case control study Setting: University hospital Ethics: Ethics approval gained Data collection: 24-pH monitoring Statistical analysis: Students t-test Pearson chi^2 or Fisher exact test	oesophus pH-monitoring reported. Outcome: OME group, control group Number with reflux: 6 of 20, 3 of 20 Episodes with pH <4 (n): 31.7 +/- 37.2, 26.7 +/- 21.0 Time when pH < 4 (RI%): 2.5 +/- 3.0, 3.2 +/- 6.3 Reflux episodes long than 5 minutes (n): 1.1 +/- 1.9, 1.4 +/- 3.1 Duration of longest episode (minutes): 8.6 +/- 10.4, 10.8 +/-22.7 No statistical difference between the groups was found	on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? Yes, but small sample size Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? Yes, based on a subtype of GORD Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes, presence of OM or not Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No. However, it is only measure of it. Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Bibi,H., Khvolis,E., Shoseyov,D., Ohaly,M., Ben,Dor D., London,D., Ater,D., The prevalence of gastroesophageal reflux in children with tracheomalacia and	**Sample size** 116 infants 41 had assessment for GER **Characteristics** Of 116 patients:	**Tests** GER tests: Either Barium meal or pH monitoring (duration not stated). Bronchial tests: Flexible bronchoscopy	**Methods** Study design: Retrospective cohort stsudy Setting: Hospital	**Results** In total 41 infants had reflux studies involving barium meal and/or pH monitoring Condition: Barium study GER+, Barium study	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
laryngomalacia, Chest, 119, 409-413, 2001 **Ref Id** 237135 **Country/ies where the study was carried out** Israel **Study type** Retrospective cohort study **Aim of the study** Determine the prevalence of GER among infants with chronic respiratory symptoms and to determine whether laryngomalacia and tracheomalacia were associated with an increase in the prevalence of GER **Study dates** July 1996 to August 1998 **Source of funding** Not stated	age ranged from 3 to 34 months, mean 16 months +/- 8 months 76 males and 40 females **Inclusion Criteria** All children underwent chest radiographs before flexible bronchoscopy **Exclusion Criteria** None stated	including lavage	Ethics: Not mentioned Positive and neagtive cases GER diagnosed if documentation of barium reflux via the gastroesophageal sphincter to the upper esophagus during barium swallow or pH < 4.0 for >8% of the duration of the pH monitoring study. Laryngomalacia defined as severe collapse of the epiglotis and arytenoids Tracheomalacia defined as narrowing of trachea with a cartilaginous to membranous ratio of 3:1 Data collection: Medical records Statistical analysis: Studennt's t-test or Chi^2	GER-, pH study GER+, pH study GER-, Barium and pH GER+, Barium and pH GER- Laryngotracheolmalacia: 9*, 3, 9, 1, 14*, 2 Tracheomalacia: 2, 6, 7, 3, 7*, 6 Laryngomalacia: 4, 7, 4, 4, 7*, 6 Control group: 11, 23, 11, 19, 16, 25 * p<0.05 compared with control group for same test	enrolled? Unknown Was a case-control design avoided? Yes, but retrospective cohort Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? Yes, based on two tests one of which is inappropriate. Is there concern that the included patients do not match the review question? Yes. Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Unknown Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					the index test? Yes Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? Yes. Use of barium meals is not used to identify GORD in current clinical practice. Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Unkown
Full citation Carr,M.M., Nguyen,A., Nagy,M., Poje,C., Pizzuto,M., Brodsky,L., Clinical presentation as a guide to the identification of GERD in children, International Journal of Pediatric Otorhinolaryngology, 54, 27-32, 2000	**Sample size** 295 charts were reviewed. **Characteristics** Of 295 children: - 214 had diagnosis of GERD after tests, 81 had no positive test for GERD. - 61% were male.	**Tests** Diagnostic tests for identifying GERD: - Gastrointestinal series, gastric scintiscan, 24 hour pH monnitoring and oesophageal biopsy 27 symptoms and signs reported, those releveant to the review were: - Feeding problems	**Methods** Setting: Depart of Pediatric Otolargyngology Data collection: Retrospective study. Data was extracted from charts. Variables collected included demongraphics, main reported symptoms and	**Results** Symptom = % GERD with symptoms (n = 214) vs % Control with symptom (n = 81) - Feeding problems = 33 vs 21 - Failure to thrive = 9 vs 0 - Choking/gagging = 24 vs 13 - Food refusal = 22 vs 21	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Ref Id 237565 **Country/ies where the study was carried out** USA **Study type** Case-control study **Aim of the study** The aim of the study was to examine frequency of aerodigestive symptoms in children with and without GERD. **Study dates** Patient charts were reviewed from October 1996 to May 1999. **Source of funding** Not stated	- 37% were aged 2 years or less. - Mean average age was 4.4 years - 66% had positive scintiscans - 40% had positive pH monitoring - 24% had positive oesophageal biopsy - 23% has positive UGIs **Inclusion Criteria** Children referred for investigation of GERD due to atypical GERD symptoms on careful history taking or evidence of reflux laryngitis on flexible fiberoptic nasopharyngolaryngoscopy. **Exclusion Criteria** Not stated	- Failure to thrive - Choking/gagging - Food refusal - Stomach ache - Chest pain - Hoarseness - Irritability - Arching - Obstructive apneoa	results of diagnostic tests (gastrointestinal series, gastric scintiscan, 24 hour pH monnitoring and oesophageal biopsy). Positive and negative cases: Positive cases were defined as having at elast one positive diagnostic test. Statistical analysis: Non-parametric tests. No further detailed provided.	- Stomach ache = 18 vs 37 - Chest pain = 12 vs 21 - Hoarseness = 34 vs 46 - Irritability = 3 vs 1 - Arching = 3 vs 0 - Obstructive apneoa = 3 vs 7 Frequent cough = 51 vs 41	inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? Yes, some of the tests used to identify GORD is not used in current clinical practice Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes, presence of symptom or not Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? No Were the reference standard results interpreted without knowledge of the results of the index test? Yes Could the reference standard, its conduct, or its interpretation have

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					introduced bias? Yes, some of tests are not used in current clinical practice. Is there concern that the target condition as defined by the reference standard does not match the review question? Yes. Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Carr,M.M., Nagy,M.L., Pizzuto,M.P., Poje,C.P., Brodsky,L.S., Correlation of findings at direct laryngoscopy and bronchoscopy with gastroesophageal reflux disease in children: a prospective study, Archives of Otolaryngology -- Head and Neck Surgery, 127, 369-374, 2001 **Ref Id**	**Sample size** 77 children **Characteristics** n = 77 51 males and 26 females Average age 4.2 years **Inclusion Criteria** All patients who underwent direct laryngoscopy and bronchoscopy	**Tests** Regions assessed and graded as none, mild or severe symptoms. Larynscopy and bronchoscopy - Lingual tonsil - Postglottic edema and erythema - Arytenoid edema and erythema - Ventricle - True vocal fold edema - Vocal fold lesions - Posterior cobblestoning Cricotrancheal region:	**Methods** Study design: Prospective cohort study Setting: Children's hospital Ethics: Not stated Data collection: GERD based on review of medical records Laryngeal based on direct diagnostic tests. Positive and negative	**Results** Symptom: GERD+, GERD - Larynx and supraglottic region Number: 50, 21 Lingual tonsil %: 70, 19 Postglottic edema and erythema %: 86, 29 Arytenoid edema and erythema %: 84, 29 Ventricle obliteration %: 38, 14 True vocal fold edema %: 70, 19 Vocal fold lesion %: 18,	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? Yes, selection was

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
245126 **Country/ies where the study was carried out** Canada **Study type** Prospective cohort study **Aim of the study** To correlate direct laryngoscopic and bronchoscopic findings with the presence of positive test results for GERD in children **Study dates** June 1999 to October 1999 **Source of funding** Not stated	**Exclusion Criteria** Not stated	- General edema and erythema - Cobblestoning - Subglottic stenosis - Blunt carina - Increased secretions - Stomal granulouma GERD: Based on review of medical records	cases: Symptoms suggestive or GERD or positive diagnostic test - pH monitoring, upper GI series or esophageal biopsy. If no positive test then put in indeterminate group. Statistical analysis: t-test for continuous Mnn-Whitney for categorical	29 Hypopharyngeal cobblestoning %: 32, 14 Cricotracheal region General edema and erythema %: 58, 19 Cobblestoning %: 42, 24 SGS %: 26, 10 Blunt carina %: 70, 10 Increased secretions %: 44, 24 Stomal granuloma %: 38 (n = 21), 0 (n = 5) Arytenoid edema, postglottic edema, enlarged lingual tonsil: At least 1 severe symptom: sensitivity 50%, specificity 100% At least 2 mild to severe: sensitivity 87.5%, specificity 68% Laryngeal score of 4 or more: sensitivity 74%, specificity 81% Cricotracheal score of 2 or more: sensitivity 82%, specificity 67% Total score 7 or more: sensitivity 76%, specificity 86% Sensitivity	based on clinical interpretation. Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? Yes, does not measure actual symptom of interest but conditins that lead to symptom. Domain 3 Is the reference standard likely to correctly classify the target condition? No, based on patient records Were the reference standard results interpreted without knowledge of the results of the index test? Yes Could the reference standard, its conduct, or its interpretation have introduced bias? Yes, based on different criteria

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Is there concern that the target condition as defined by the reference standard does not match the review question? No. Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Unknown
Full citation Chang,A.B., Cox,N.C., Faoagali,J., Cleghorn,G.J., Beem,C., Ee,L.C., Withers,G.D., Patrick,M.K., Lewindon,P.J., Cough and reflux esophagitis in children: their co-existence and airway cellularity, BMC Pediatrics, 6, 4-, 2006 **Ref Id** 245155 **Country/ies where the study was carried out** Australia	**Sample size** 163 approached 150 agreed to enter study **Characteristics** aged range: 0.8 to 16 years, mean 8.2 years Sex: 91 boys Primary indications: - abdominal pain = 77 - recurrent vomiting = 35 - poor weight gain = 20 - review of previous lesion = 19 - choking = 17	**Tests** Cough Assessed on a validated VAS from 0 (no cough) to 10 (severe cough). Scored repeated within 3 weeks. GORD Histology of oesophageal biopsy showed reflux esophagitis (basal cell hyperplasia and mucosal inflammatory neutrophilic infiltrate, with <=5 eosinophils per high power field).	**Methods** Study design: Prospectice cohort Setting: Not stated Ethics: Local ethics approval and written consent Data collection: All children scheduled for elective esophago-gastroscopy. Symptom questionnaire completed twice within a 3 week period to determine repeatability of results.	**Results** Outcome presence of cough and RE Cough+ Reflux Esophagitis+ = 33 Cough+ Reflux Esophagitis- = 36 Cough- Reflux Esophagitis+ = 44 Cough- Reflux Esophagitis- = 37	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study type Prospective cohort study **Aim of the study** Hypothesised that in children without an underlying lung disease, cough is more likely to be present in children with RE than those without RE and, are more likely to have airway neutrophilia. **Study dates** September 2002 and May 2004 **Source of funding** Royal Children's Hospital Foundation grant National Health and Medical Research Council grant	**Inclusion Criteria** All children undergoing elective esophago-gastroscopy based on suspicion of GERD determined by symptoms - regurgitation, acid brash, heartburn and/or meal related discomfort. **Exclusion Criteria** Neuro-developmental abnormalities Clinical history of primary aspiration Cardio-respiratory disease		Positive and negative cases: Histology of oesophageal biopsy showed reflux esophagitis (basal cell hyperplasia and mucosal inflammatory neutrophilic infiltrate, with <=5 eosinophils per high power field). Cough based on reported symptoms of > 4 weeks with any GERD symptoms and scored >= 2 on the cough visual analog scale. Statistical analysis: Chi^2 to compare categorical data		No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No. However, it is only measure of it. Domain 4 Was there an appropriate interval between index

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Chopra,K., Matta,S.K., Madan,N., Iyer,S., Association of gastroesophageal reflux (GER) with bronchial asthma, Indian Pediatrics, 32, 1083-1086, 1995 **Ref Id** 245175 **Country/ies where the study was carried out** India **Study type** Case-control study **Aim of the study** Evaluation of association of GER with bronchial asthma and its relation with nocturnal exacerbation of symptoms and the effect of	**Sample size** 80 children with bronchial asthma - case 10 children without asthma - control **Characteristics** Cases: Age 9 months to 12 years, mean 6.55 (+/- 3.65) years Control: Age 9 months to 8 years, mean 4.5 (+/- 2.16) years **Inclusion Criteria** - Bronchial asthma - 3 or more episodes of reversiable bronchospasm **Exclusion Criteria** Evidence of pulmonary tuberculosis, emphysema or	**Tests** Scintiscan	**Methods** Study design: Case-control Ethics: No mentioned Data collection: Scintiscan Positive and negative cases - Positive case when tracer seen in oesophagus for more than 2 frames - Negative if no reflux tracer was seen in the oesophagus Statistical analysis: Not stated	**Results** Ashtma+ Scintiscan+ = 31 Ashtma+ Scintiscan- = 49 Ashtma- Scintiscan+ = 0 Ashtma- Scintiscan- = 10	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? Unknown Is there concern that the included patients do not match the review question? Yes, based on a test that is not used in current clinical practice Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
bronchodilator therapy on GER **Study dates** Not stated **Source of funding** Not stated	other known lung or heart disease.				unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? No, test is no longer used in clinical practice Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? Yes. Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes Did patients receive the same reference standard?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Contencin,P., Narcy,P., Gastropharyngeal reflux in infants and children. A pharyngeal pH monitoring study, Archives of Otolaryngology -- Head and Neck Surgery, 118, 1028-1030, 1992 **Ref Id** 245201 **Country/ies where the study was carried out** France **Study type** Case-control study **Aim of the study** - Demonstrate possible phayngeal involvement in GER through local 24-hour pH moniotring - Establish the possible relationship between this involvement and a local recurrent inflammatory process	**Sample size** 8 cases 6 controls **Characteristics** **Inclusion Criteria** Cases: children referred for recurrent croup Controls: Children in hospital for post surgical recovery No hisotry of lartngitis or pharyngitis Pharyngolarnyges clinically normal **Exclusion Criteria** None stated	**Tests** 24-hour pH monitoring using digitrapper Laryngeal conditions based on previous clinical diagnosis	**Methods** Study design: Case-control Setting: Not stated Ethics: Parental consent obtained Positive and negative GERD Reflux index of 5.2% for pH <4 and 12% for <5 Statistical analysis: Mann-Whitney U test for non-parametric data	**Results** Group: GOR+, GOR- Patients: 5, 3 Controls: 1, 5	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? Yes, controls recovering from surgery Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? unknown If a threshold was used, was it pre-specified? Unknown, croup was based on clinical decision Could the conduct or interpretation of the index

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study dates Not stated **Source of funding** Egic-Jouille Foundation research grant					test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No. however, it is only measure of it. Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Small sample size
Full citation Deal,L., Gold,B.D., Gremse,D.A., Winter,H.S., Peters,S.B., Fraga,P.D., Mack,M.E., Gaylord,S.M., Tolia,V., Fitzgerald,J.F., Age-specific questionnaires distinguish GERD symptom frequency and severity in infants and young children: development and initial validation, Journal of Pediatric Gastroenterology and Nutrition, 41, 178-185, 2005 **Ref Id** 237854 **Country/ies where the study was carried out** USA **Study type** Case-control study **Aim of the study** 1) confirm appropriateness of GERD symptoms used in a questionnaire 2) test range of measurements of scales 3) test ease of completion of questionnaire 4) confirm symptoms	**Sample size** Infants age 1 to 11 months: 23 healthy controls and 41 with GERD Yong children: 27 healthy controls and 40 with GERD **Characteristics** Infants: Healthy vs GERD Age (months), Mean (SD): 5.1 (3.1), 5.6 (2.5) Sex (Male, %): 39%, 59% Method of diagnosis of GERD Healthy - Not defined GERD - Symptoms (98%), Upper GI study (22%), pH monitoring (15%), endoscopy with histology (9.8%) Young children Age (months), Mean (SD): 31.3 (14.8), 30.0 (12.1) Sex (Male %): 52%, 60% Method of diagnosis of GERD Healthy - Not defined GERD - Symptoms (92.5%), endoscopy with histology (37.5%), Upper GI study (22.5%), pH monitoring (10%) **Inclusion Criteria** Children upto the age of 5 GERD groups had symptoms or test results demonstrating likely presence of GERD	**Tests** Questionnaires (GSQ-I and GSQ-YC) investigating reported symptoms reported in the previous 7 days, including frequency.	**Methods** Ethics approval obtained for study. Questionnaire completed by parent/guardian at visit to site.	**Results** **Infants (1 to 11months)** Proportion of children reporting symptoms Arching back 27/41 vs 5/23, p = 0.001 Choking/Gagging 31/41 vs 8/23, p < 0.001 Hiccup episodes 35/41 vs 13/23, p = 0.016 Irrability/Fussiness 29/41 vs 5/23, p < 0.001 Refusal to feed 17/41 vs 4/23, NS Vomiting regurgitation 37/41 vs 13/23, p = 0.003 Number of episodes Arching back 12.3 (19.3) vs 1.1 (3.1)= 0.001 Choking/Gagging 12.9 (24.2) vs 2.2 (6.0), p < 0.001 Hiccup episodes 8.8 (13.2) vs 2.6 (3.5), p = 0.016 Irratitability/Fussiness , 6.7 (9.6) vs 1.4 (3.4) p < 0.001 Refusal to feed 2.8 (5.6) vs 0.6 (1.7), NS Vomiting regurgitation 30.6 (43.9) vs 3.7 (9.0), p = 0.003 Severity of symptom (1 [Best] to 7 [worst] - data not presented in paper	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? Yes, controls were not tested for presence of GORD. Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
scores were higher in children with GERD than those without. **Study dates** Not stated, but submitted for publication in 2004 **Source of funding** Wyeth pharmaceuticals	Control groups had a "well visit" to clinic with no GI complaints. No restriction on prior medication **Exclusion Criteria** Children aged 5 years or more			only p-values) Arching back, p= 0.014 Choking/Gagging, p = 0.028 Hiccup episodes, p = 0.002 Irratitability/Fussiness , p = 0.051 Refusal to feed, NS Vomiting regurgitation, p < 0.001 Individual symptom score (number of episodes and severity) Arching back 58.3 (101.6) vs 1.9 (5.9), < 0.001 Choking/Gagging 71.0 (162.4) vs 6.1 (18.0), p < 0.001 Hiccup episodes 42.4 (87.3) vs 5.0 (7.6), < 0.001 Irratitability/Fussiness , 35.5 (56.1) vs 3.8 (12.7) p < 0.001 Refusal to feed 14.1 (31.8) vs 3.7 (9.0), NS Vomiting regurgitation 151.9 (222.9) vs 11.5 (43.4), < 0.001 Composite score of all questions using a cut-off of >27 found sensivity of 90% and specificity of 83% **Young children**	Domain 3 Is the reference standard likely to correctly classify the target condition? No, control group could have GORD as not tested. Were the reference standard results interpreted without knowledge of the results of the index test? Yes, undertaken before survey Could the reference standard, its conduct, or its interpretation have introduced bias? Yes Is there concern that the target condition as defined by the reference standard does not match the review question? No. Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? No Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No Study GERD populations based on clinical symptom rather than objective measure. This biases the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Addominal/Belly pain 17/40 vs 1/27, p =0.001 Burping/Belching 27/40 vs 10/27, p =0.001 Choking when eating 23/40 vs 1/27, p <0.001 Difficulty swallowing 14/40 vs 0/27, p <0.001 Refuses to eat 25/40 vs 7/27, p =0.003 Vomiting/regurgitation 22/40 vs 3/27, p <0.001 Table missing from paper showing number of episodes and individual symtpoms scores CSS > 8 had a sensitivity of 85% and specificity of 81.5%	results as GERD is based on the symptoms collected in the questionnaire.
Full citation El-Serag,H.B., Gilger,M., Kuebeler,M., Rabeneck,L., Extraesophageal associations of gastroesophageal reflux disease in children without neurologic defects, Gastroenterology, 121, 1294-1299, 2001 **Ref Id** 245305 **Country/ies where the study was carried out**	**Sample size** 1980 GERD patients 7920 controls without GERD **Characteristics** Characteristic: GERD group, Controls Age (years), mean +/- SD: 9.16 (4.61), 8.64 (4.92) Gender male: 969, 4173 **Inclusion Criteria** Cases: Children with coding of GERD	**Tests** Based on ICD-9 coding of GERD (530.81, 530.10, 530.11, 530.19, 530.3)	**Methods** Study design: Retrospective case-control study Ethics: No mentioned Data collection: Based on electronic medical records from children's hospital database Positive and negative cases: Based on clinical coding for condition.	**Results** Outcome: GERD group (n = 1980), Controls (n = 7920), Odd ratio (95% CI), p-value, adjusted Odds Ratio (age, gender and ethnicity) Sinustitis: 83, 107 3.19 (2.38 to 4.27), <0.0001, 2.34 (1.72 to 3.19) Otitis media: 41, 366, 0.44 (0.31 to 0.61), <0.0001, 0.40 (0.28 to 0.55) Laryngitis: 14, 15, 3.75 (1.81 to 7.79), 0.0001, 2.62 (1.20 to 5.64) Asthma: 261, 535, 2.10	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
USA **Study type** Case-control study **Aim of the study** Association between GERD and several predefined potential extraesophageal manifestations of GERD **Study dates** October 1996 to October 2000 **Source of funding** Eisai Inc and Janssen Pharmaceutica	Controls: Without GERD **Exclusion Criteria** Cerebral palsy Mental retardation Tracheoeosophageal congenital abnormalities Congenital esophageal stenosis		Statistical analysis: X^2 and t-tests for univariate analysis.	(1.79 to 2.45), <0.0001, 1.93 (1.63 to 2.28) Pneumonia: 124, 180, 2.87 (2.27 to 3.63), <0.0001, 2.28 (1.77 to 2.93) Bronchiectasis: 19, 19, 5.84 (3.20 to 10.68), <0.001, 2.28 (1.14 to 4.57)	included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? No, based on clinical records Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes, but likely to be variance. Were the reference standard results interpreted without knowledge of the results of the index test? No, but based on retrospective review Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? No, control group selected based not being coded with GORD Did patients receive the same reference standard? Unknown Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Ersin,N.K., Oncag,O., Tumgor,G., Aydogdu,S., Hilmioglu,S., Oral and dental manifestations of gastroesophageal reflux disease in children: a preliminary study, Pediatric Dentistry, 28, 279-284, 2006 **Ref Id** 238132 **Country/ies where the study was carried out** Turkey **Study type** Case-control study	**Sample size** 38 with GERD 42 matched healthy controls **Characteristics** Characteristic: GERD, Controls N: 38, 42 Mean age years (SD): 6.5 (3.6), 6.9 (2.8) Sex male: 19, 21 Salivary buffering capacity: High: 25, 33 Medium: 7, 8 Low: 6 , 1 **Inclusion Criteria** Controls - GERD established by pH monitoring Cases - age and gender	**Tests** GORD: pH monitoring Dental: Caries based on WHO criteria. Erosion based on Eccles and Jenkins index	**Methods** Study design: Case-control study Setting: Pediatric gastroenterology patients at university hospital Ethics: Ethics approval obtained and parental consent obtained. Data collection: GORD based on previous clinical classification Dental recorded by 2 independent examiners Statistical analysis: Mann-Whitney and	**Results** Outcome: GERD subjects (n = 38), Control subjects (n = 42) Erosion prevalence (%): 29, 10* Severe erosion: 37, 5* Caries prevalence: 27, 31* * significant at $p < 0.05$	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aim of the study Investigate GERD's effects on erosion, caries formation, salivary function and salivary micorbiological counts compared to healthy controls. **Study dates** Not stated **Source of funding** Not stated	matched undergoing dental examination **Exclusion Criteria** Not taking antibiotics in previous 3 months		Spearman rank used for differences between groups. Chi^2 or Fisher's exact test used for categorical variables.		interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No. Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Unknown

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No - Unclear if controls were tested for GORD - pH confirmation of GORD cases not specified
Full citation Frakaloss,G., Burke,G., Sanders,M.R., Impact of gastroesophageal reflux on growth and hospital stay in premature infants, Journal of Pediatric Gastroenterology and Nutrition, 26, 146-150, 1998 **Ref Id** 245390 **Country/ies where the study was carried out** USA **Study type** Case-control study **Aim of the study** To understand better the potential impact of GER on growth in premature infants.	**Sample size** 23 cases with GER and 23 controls **Characteristics** Premature infants < 37 weeks. Reflux index in cases mild < 10% = 1 moderate 10-20% = 14 severe 20>% = 6 **Inclusion Criteria** Cases: Premature < 37 weeks Clinically significant GER Controls: Matched for gestational age, birth weight, gender, and bronchopulmonary dysplasia.	**Tests** Test for GER not stated Weight gain based on chart review	**Methods** Study design: Restrospective case-control study Setting: NICU	**Results** Days until regained birth weight: Cases = 19 days +/- 5 days vs controls = 16 day +/- 7 days, p = 0.12 Average weekly weight gain: No difference.	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? Yes, children treated in NICU Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study dates January 1990 to December 1993 **Source of funding** Not stated	**Exclusion Criteria** Gastrointestinal tract anomalies Severe neurologic disease Surgical treatment of necrotiz=sing entercolitis Chromosomal abnormalities Malformations impairing feeding Transferred to another hospital Died during treatent				If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Unknown, test not defined Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No. Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Unknown Did patients receive the same reference standard? Unknown

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Ghaem,M., Armstrong,K.L., Trocki,O., Cleghorn,G.J., Patrick,M.K., Shepherd,R.W., The sleep patterns of infants and young children with gastro-oesophageal reflux, Journal of Paediatrics and Child Health, 34, 160-163, 1998 **Ref Id** 237721 **Country/ies where the study was carried out** Australia **Study type** Case-control study **Aim of the study** Compare sleep patterns data in children categorized with or without GORD as defined by 24-hour pH monitoring. **Study dates** Not stated	**Sample size** 113 consecutive children 102 consented to join study Compared with 3102 children from a previous study. **Characteristics** **Inclusion Criteria** Consecutive children less than 3 years old referred for pH monitoring for GORD **Exclusion Criteria** Not stated	**Tests** 254 hour pH monitoring using a DigiTrapper. Sleep pattern questionnaire used in well baby screening test	**Methods** Study design: Case-control study Setting: Children's hospital Ethics: Ethical approval gained and parent consent obtained Positive and negative cases of GORD: A fractional RI > 95% centile for age with an oesophageal pH of below 4.0. Patient recruitment: Consecutive children attending clinic for suspected GORD Children involved in a separate sleep pattern study Data collection: pH monitoring Questionnaire Statistical analysis: Chi^2	**Results** Outcome: Normal population (n = 3102), GOR- (n = 26), GOR+ (n = 76) Proportion (%) having a daytime sleep 1-3 months: 88.1, 100, 96 3-12 months: 86, 90, 86 12-24 months: 75, 71, 65 24-36 months: 31, 40, 63 Proportion (%) where length of day sleep > 2 hours 1-3 months: 48, 0 , 0* 3-12 months: 18, 20, 25 12-24 months: 21, 20, 21 24-36 months: 16, 15, 0 * p<0.05 for normal vs GOR+ Proportion (%) sleeping at night without intervention 1-3 months: 30, 0, 0 3-12 months: 45, 0*, 18* 12-24 months: 45, 18*, 8** 24-36 months: 56, 10*, 4* * p<0.05 for comparison with normal group ** P<0.01 for comparison with normal group and GOR- group	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Consecutive Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes, but unknown if used on control subjects Could the conduct or interpretation of the index test have introduced bias? No

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding Not stated				Proportion (%) waking > 3/night > 2 hours per night 1-3 months: 7, 0, 100 3-12 months: 13, 33*, 50** 12-24 months: 10, 45*, 60* 24-36 months: 3.5, 14*, 50** * p<0.05 for comparison with normal group ** P<0.01 for comparison with normal group and GOR- group	Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No. Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Unknown in the control group, but study also compared + & - tests in those tested. Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Gustafsson,P.M., Kjellman,N.I., Tibbling,L., Bronchial asthma and acid reflux into the distal and proximal oesophagus, Archives of Disease in Childhood, 65, 1255-1258, 1990 **Ref Id** 237009 **Country/ies where the study was carried out** Sweden **Study type** Prospective cohort study **Aim of the study** Investigate the prevalence of pathological gastro-oesophageal reflux in children and adolescents with asthma by 24-hour pH moniotring, and to study the correlation between symptoms of asthma and relfux into the distal and proximal oesophagus. **Study dates** Not stated	**Sample size** 55 assessed and 42 recruited. **Characteristics** - n = 42 - Mean age 13.7 years (range 9.0 to 20.0) - 25 boys/ 17 girls - All receiving treatment for asthma - 35 had atopic asthma - allergy mediated. **Inclusion Criteria** Moderate to severe asthma - bronchial asthma severe enough to restrict daily activities for a total of at least 10 days during previous year. **Exclusion Criteria** Not stated	**Tests** 24-hour pH monitoring	**Methods** Study design: Prospective cohort study Ethics approval: Ethics approval gained and written consent from parents. Data collection: 24-hour pH monitoring Positive & negative cases: 95% CI of distal reflux time (pH < 4) was 1% in a healthy control group. Statistical analysis: Mann-Whitney test Fisher's exact square	**Results** 21 of 42 children had a pathological total reflux time (>1.0%) in the distal oesohagus. A separate study report 4 of 27 children wothout asthma had reflux time (>1%). Variable: Asthmatics, Controls Distal % RI time, mean (SD): 1.52 (1.42), 0.47 (0.39), p < 0.001 Proximal % RI time, mean (SD): 0.34 (0.29), 0.13 (0.17), p < 0.001 Distal number of reflux episodes per hour: 0.95 (0.70), 0.43 (0.34), p < 0.001 Proximal number of reflux episodes per hour: 0.29 (0.27), 0.15 (0.20), p < 0.05 Distal duration of longest episdoe (minutes): 5.03 (7.10), 1.69 (1.22), p < 0.001 Proximal duration of longest episdoe (minutes): 1.39 (1.09), 0.72 (0.97), p < 0.001	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding Not stated					likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No, but only one test for condition. Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Unknown Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No **Other information** Figures for control group taken from a separate study undertaken by same authors using same methods on healthy children. Found a prevalence of 4 of 27 had

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					proximal pH > 1% above 95% normal range.
Full citation Heine,R.G., Jordan,B., Lubitz,L., Meehan,M., Catto-Smith,A.G., Clinical predictors of pathological gastro-oesophageal reflux in infants with persistent distress, Journal of Paediatrics and Child Health, 42, 134-139, 2006 **Ref Id** 237724 **Country/ies where the study was carried out** Australia **Study type** Prospective cohort study **Aim of the study** Identify clinical predictors of pathological GOR in infants with persistent crying that may assist in identifying infants at risk of reflux-related complications. **Study dates** Consecutive chuildren seen between March 1995 and	**Sample size** 208 children enrolled. 16 - had identifiable condition so were excluded 36 - withdrawn by their parents 5 - pH monitor failed so no data available. 151 - included in final data analysis **Characteristics** Of the 151 children included in the data analysis. - median age was 2.5 months, range 0.5 to 8.2 months - 82 were males - 91 were aged under 3 months No statistical difference was found in the demographic charactieristics of those included and those excluded from the analsysis. **Inclusion Criteria** Children admitted to hospital with persistent distress Aged under 9 months **Exclusion Criteria** Identifyiable cause of distress	**Tests** Diagnostic tests used: 24-hour pH monitoring performed on day 2 using a Mark-III Digitrapper. Reflux medications were ceased at least 48 hours before the monitoring. Symptoms recorded using a diary: - Feeding difficulties, unspecified - Refusing feeding when hungry - Backarching	**Methods** Design: Prospective cohort study Ethics approval: Local hospital ethics approval Writtern consent from parents of infants Setting: Hospital Data collection: Consecutive infants addmitted for investigation were recruited. Oesophageal pH-monitoring using a Mark-III Digitrapper. 24-hour cry/fuss chart completed by nursing staff adapted I-GERQ symptoms questionnaire completed by parents Positive and negative cases: Positive cases defined as percentage of time with an oesophageal pH < 4.0. A fractional reflux time of greater than 10% was considered abnormal.	**Results** Symptoms recorded using a diary: n(%), Sensitivity, Specificity, PPV, NPV, Odds ratio, 95% CI, p-value - Feeding difficulties, unspecified: 81 (57), 75.0, 46.2, 22.2, 90.0, 2.57, 0.89; 8.44, 0.06 - Refusing feeding when hungry: 62 (43), 45.8, 57.5, 17.7, 84.1, 1.14, 0.44; 3.00, 0.76 - Backarching: 84 (57), 72.0, 45.5, 21.4, 88.7, 2.14, 0.77; 6.14, 0.11	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Consecutive Was a case-control design avoided? No Did the study avoid inappropriate exclusions? No, high dropout rate of 25% Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes, but based on cquestionnaire Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
June 1998. **Source of funding** Grants from Royal Children's Hospital Research Institute, the Katherine Mothercraft Scoiety and the J. Reid Charitable Trust.			Statistical analysis: pH monitoring results were compared using X2-test		review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No, but only one test for GORD Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Unknown Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Koda,Y.K., Ozaki,M.J., Murasca,K., Vidolin,E., Clinical features and	**Sample size** 307 children referred for pH monitoring	**Tests** pH monitoring using Mk III Digitrapper in an in-patient setting.	**Methods** Setting: Pediatric Gstroenterology Service	**Results** Symptoms: normal pH (n = 251), abnormal pH (n = 56)	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
prevalence of gastroesophageal reflux disease in infants attending a pediatric gastroenterology reference service, Arquivos de Gastroenterologia, 47, 66-71, 2010 **Ref Id** 237064 **Country/ies where the study was carried out** Brazil **Study type** Retrospective cohort study **Aim of the study** Describe some of the clinical aspects of GERD associated with acid reflux and to determine its prevalence in a population of infants. **Study dates** December 1998 to December 2008 **Source of funding** Not stated	**Characteristics** Wholre group: Age (mean +/- SD): 12.2 +/- 6.2 months (range 1 to 23 months) Sex: 124 (40.4%) females Clinical manifestations: - Digestive = 62 - Respiratory = 120 - Crisis of cyanosis = 42 - Mixed = 65 - Other = 18 **Inclusion Criteria** Children undergoing pH monitoring **Exclusion Criteria** - Incomplete pH monitoring - Using bronchodilators, corticosteriods or antibiotics - Anti-reflux symptoms within 3 days or PPIs within 7 days. - History of neurological impairment or congenital gastrointestinal disease - Previous surgery of oesophagus or stomach	Symptoms: - Digestive = regurgitation and vomiting - Respiratory = stridor, wheezing, etc. - Crisis of cyanosis - Mixed - Other = failure to thrive, distress, etc.	Ethics: Not stated Data collection: Results from patient charts Positive and negative cases: Abnomral reflux based on Reflux Index (>10% for infants of 0 to 12 months of age and >6% for those of 13 to 24 months). Statistical analysis: - Fisher's test for dichotomous outcomes.	Digestive: 47 vs 15 Respiratory: 105 vs 15 Cyanosis: 32 vs 10 Mixed: 51 vs 14 Others: 16 vs 2 pH outcomes: normal pH (n = 251), abnormal pH (n = 56) RI (%): 3.0 +/- 2.3 vs 13.1 +/- 6.8 No. episodes 24 hours: 30.4 +/- 21.6 vs 58.4 +/- 24.5 Duration of longest episodes (minutes): 7.8 (+/- 7.7) vs 35.2 (+/- 28.6)	Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? Yes, but a retrospective study Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes, data extracted from charts Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No. Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Unknown Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Kotsis,G.P., Nikolopoulos,T.P., Yiotakis,I.E., Papacharalampous,G.X., Kandiloros,D.C., Recurrent acute otitis media and gastroesophageal reflux disease in children. Is there an association?, International Journal of	**Sample size** 221 children assessed, and 34 excluded: Group A RI <4.5: 49 Group B RI 4.5 to 20%: 78 Group C RI >20%: 60 **Characteristics** Group A RI <4.5	**Tests** Reflux monitoring 24 hour ambulatory pH monitoring Mk II Digitrapper. Otitis Media: - At least 3 episodes of acute Otitis Media in a 6-month period or four episodes per year with free intervals of at least 1 month	**Methods** Setting: Not stated, but study authors work in hospital setting Ethics: Not stated Data collection: pH monitoring	**Results** Reflux group: OM negative, OM positive A: 43, 6 B: 67, 11 C: 41, 19 Odds ratio: A vs B = 1.1 (0.3 to 3.6) A vs C = 4.0 (1.3 to 11.6)	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Pediatric Otorhinolaryngology, 73, 1373-1380, 2009 **Ref Id** 219929 **Country/ies where the study was carried out** Greece **Study type** Prospective cohort study **Aim of the study** The aim of this study is to investigate whether there is a relationship between GERD and recurrent acute Otitis Media in infants and children. **Study dates** Not stated **Source of funding** Not stated	Mean age: 19.7 months Sex: 26 boys Group B RI 4.5 to 20% Mean age: 17.6 months Sex: 37 boys Group C RI >20% Mean age: 17.9 months Sex: 33 boys **Inclusion Criteria** Children presenting with symptoms and signs of GERD: - Regurgitation or vomiting - Poor appetite - Failure to thrive - Apneoa - Chronic cough - Wheezing - Asthma - Excessive hiccups - Seizures - Irratiability **Exclusion Criteria** Age younger than 40 days or oldr than 3 years Neurological deficits - cerebal palsy, mental retardation, neurological syndrome) Congenital abnormalities - Cleft lip, etc. Chronic systemic disorders - cystic fibrosis, etc		undertaken by authors Parental diary of symptoms Otitis media followed-up over 6 to 8 year period from medical records and NHS records Positive or negative cases of GORD: - Controls had RI < 4.5% - Mild-moderate had RI 4.5 to 20% - Severe had RI > 20% Otitis media: - At least 3 episodes of acute Otitis Media in a 6-month period or four episodes per year with free intervals of at least 1 month Statistical analysis Chi-squared analysis		Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Yes, presence of condition based on medical records. Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No, but only one measure of GORD Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Unknown Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Linnett,V., Seow,W.K., Connor,F., Shepherd,R., Oral health of children with gastro-esophageal reflux disease: a controlled study, Australian Dental Journal, 47, 156-162, 2002 **Ref Id** 245790 **Country/ies where the study was carried out**	**Sample size** 104 childre: 52 with GERD; 52 simblings **Characteristics** Characteristic: GORD, Control Total number: 52, 52 Number girls: 21, 25 Mean age years (SD): 6.5 (4.1), 9.25 (4.2) **Inclusion Criteria** Cases:	**Tests** GORD Histological diagnosis of reflux oesophagitis and biopsy using endoscopy. Details not provided. Dental examination Single examiner using Gingival INnflammation Index; Modified Plaque Index; WHO caries criteria; FDI Index of developmental defects of enamel; and Erosion criteria outlined by Aine et al. Saliva sample gained using cotton swab.	**Methods** Study design: Case-control study Setting: Children's Hospital Ethics approval: Local ethics committee and parental consent. Data collection: GORD already diagnosed. Children invited for dental examination.	**Results** Prevalence of erosion: GORD vs controls Overall number of teeth with erosion: 14% vs 10%, p = 0.005 Severity of erosion: GORD vs controls Grade 1: 12 vs 20, p = 0.05 Grade 2: 45 vs 71 Grade 3: 43 vs 9, p < 0.001 Prevalence of caries: GORD vs control	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Australia **Study type** Case-control study **Aim of the study** The aim of this study was to investigate the oral health of children with GERD compared to healthy siblings. **Study dates** Not stated **Source of funding** Not stated	Confirmed GERD Controls: Siblings of cases **Exclusion Criteria** None stated		Positive and negative cases of GORD: Cases where based on histological and endoscopic examination. Controls were not tested. Statistical analysis: Student's t-test and Chi^2	Caries free: 56% vs 62% Decayed, missing or filled teeth: 9.7 vs 6.2, p < 0.001	Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? Yes, those in control group not tested but assumed not to have GORD. Is there concern that the target condition as defined by the reference standard does not match the review

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					question? No. Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? No Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Mathisen,B., Worrall,L., Masel,J., Wall,C., Shepherd,R.W., Feeding problems in infants with gastro-oesophageal reflux disease: a controlled study, Journal of Paediatrics and Child Health, 35, 163-169, 1999 **Ref Id** 219486 **Country/ies where the study was carried out** Australia **Study type** Case-control study	**Sample size** 40: 20 cases of GORD; 20 healthy controls **Characteristics** Variable: GORD group (n = 20), Control group (n = 20) Age in years, mean (SD): 0.53 (0.05), 0.54 (0.05) Gender male: 10, 11 **Inclusion Criteria** GORD cases: Attended Children's Hospital for management of GORD 24-hour pH monitoring (acid exposure > 95th centile) and endoscopic evaluation (microscopic biopsy confirmation of changes of	**Tests** GORD test by pH monitoring and endoscopic evaluation. Neither method described in detail Feeding symptoms recorded 24 hour Feeding Assessment Schedule.	**Methods** Study design: Case-control study Ethics: Ethics approval gained and informed consent from parents. Data collection: Standardised questionnaires Data analysis: Student's t-test Mann-Whitney Chi^2 test	**Results** Outcome: GORD group, Control group Vomiting at testing: 20 vs 0 (p < 0.00) Respiratory symptoms (wheezing): 11 vs 2, p < 0.011 Reported swallowing problems: 14 vs 7, p < 0.001 Crying/miserable with feeds: 17 vs 4, p <0.001 Feeding refusal behaviours Head aversion: 21.7 vs 10.8, p = 0.026 Facial grimaces: 34.4 vs 21.6, p = 0.022 Body withdrawal: 20.7 vs 6.3, p = 0.02	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aim of the study Study the nature of feeding and swallowing problems in in fants with GORD and to investigate the impact of these problems on their caregivers. **Study dates** Not stated **Source of funding** Not stated	GORD) Control group: Attended well baby clinic at Children's Hospital No evidence of GORD **Exclusion Criteria** GORD group: Premature < 37 weeks Pathology - cystic fibrosis or cerebral palsy Control group: None stated				interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? Yes, those in the control group not formally tested Is there concern that the target condition as defined by the reference standard does not match the review question? No. Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					reference standard? Unknown Did patients receive the same reference standard? No Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Mezzacappa,M.A., Rosa,A.C., Clinical predictors of abnormal esophageal pH monitoring in preterm infants, Arquivos de Gastroenterologia, 45, 234-238, 2008 **Ref Id** 237063 **Country/ies where the study was carried out** Brazil **Study type** Case-control study **Aim of the study** To identify the factors associated with increased acid oesophageal exposition in preterm infants using intra-oesophageal pH assessment during	**Sample size** 235 pH monitoring studies in 193 preterm infants: 87 cases and 87 controls **Characteristics** Variable: Cases vs controls Gestational age (weeks): 28.9 (+/- 2.2) vs 29.0 (+/- 2.5) Female (n): 44 vs 32 Birthweight (g): 1185 (+/- 290) vs 1050 (+/- 310) **Inclusion Criteria** Birthweight < 2000g Gestational age ≤ 37 weeks pH studies routinely undertaken in neonates where GERD suspected, except in patients where vomiting and regurgitation were the only symptoms and in pre-term infants with severe neurological impairment.	**Tests** Diagnostic tests used: 24-hour pH monitoring performed on day 2 using a Mark-III Digitrapper. Reflux medications were ceased at least 48 hours before the monitoring. Symptom information collected, but source of this information was not specified. The symptoms of interest were: - Small for Gestational Age - Apneoa - Acute Respiartory Distress - Feeding intolerance	**Methods** Design: Retrospective case-control study Setting: Hospital Data collection: Source of information is not specified Positive and negative cases: Cases defined as symptoms suggestive of GERD and reflux index ≥ 10% Controls defined as investigated for GERD but relfux index < 10% Statistical analysis: pH monitoring assessed using chi-squared test	**Results** Symptom: Cases (n = 87) vs controls (n = 87) - Small for Gestational Age: 34 vs 44 - Apneoa: 82 vs 76 - Acute Respiartory Distress: 72 vs 65 - Feeding intolerance: 62 vs 52	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions? No, study numbers do not match Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? Yes, set on a neonatal unit Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
hospitalisation in a neonatal unit. **Study dates** October 1995 to May 2002 **Source of funding** Not specified	**Exclusion Criteria** Excluded if monitoring undertaken in non-standardised conditions or when technical problems were encountered.				Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Unknown Did patients receive the same reference standard? No Were all patients included in the analysis? Unknown, numbers do not match

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					between inclusion and analysis. Could the patient flow have introduced bias? No
Full citation Mousa,H., Woodley,F.W., Metheney,M., Hayes,J., Testing the association between gastroesophageal reflux and apnea in infants, Journal of Pediatric Gastroenterology and Nutrition, 41, 169-177, 2005 **Ref Id** 237852 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** Determine if apnoea is associated with GER. **Study dates** Not stated	**Sample size** 25 **Characteristics** Of 25 infants Gender male: 10 Age (months): 4 (1 to 19) **Inclusion Criteria** Suspected GER **Exclusion Criteria** Not stated	**Tests** ALTE defined as combination of apnoea, colour change, change in muscle tone, choking or gagging. Reflux assessed using: MII/pH Apnoea assessed using pneumonography: nasal air flow, oxygen saturation, heart rate, electrocardiogram and chest movements.	**Methods** Study design: Prospectiive cohort study Ethics: Ethics approval and informed consent gained Statistical analysis: X^2, Mantel Haenszel, and regression analysis for time-series analysis	**Results** 80 of 527 apnoea events were temporally linked with GER (within 5 minutes). Apneoa temporally (5 minutes) associated with GER in 4 of 25 patients. (R^2 = 0.05). No association between apnoea and GER for whole group (p = 0.214).	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding NIH grant					interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No, but only one measure of GORD Domain 4 Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation O'Reilly,R.C., He,Z., Bloedon,E., Papsin,B., Lundy,L., Bolling,L.,	**Sample size** 509 cases with OM 64 controls without OM	**Tests** GORD assessed based on medical records - "objectively" identified	**Methods** Study design: Case-control study	**Results** Otitis Media GERD: 26 of 509 Cochlear implant	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Soundar,S., Cook,S., Reilly,J.S., Schmidt,R., Deutsch,E.S., Barth,P., Mehta,D.I., The role of extraesophageal reflux in otitis media in infants and children, Laryngoscope, 118, 1-9, 2008 **Ref Id** 245955 **Country/ies where the study was carried out** USA **Study type** Case-control study **Aim of the study** Designed to determine if the incidence of gastric pepsin in the middle ear is significantly greater in children with OM compared with those without OM and to examine the association of pepsin in the middle ear cleft with other factors in a large study population. **Study dates** Not stated	**Characteristics** Characteristic: Cases of OM, Controls Age (years): 4.8 (+/- 4.2), 2.7 (+/- 2.4) Sex (M/F): 33/31, 281/228 Allergy: 2, 14 Asthma: 2, 19 **Inclusion Criteria** Case - scheduled for myringotomy with tube placement for OM Controls - underwent cochlear implantation with no history of OM **Exclusion Criteria** None stated		Setting: Children's Hospital Ethics: Ethics approval gained and informed consent. Data collection: Fluid sampling at time of myringotomy and cochlear Pepsin Assay Western Blot analysis Data extraction from electronic medical records Positive and negative cases GORD based on "objectively" confirmed in medical notes Otitis media based on being scheduled for bilateral myringotomy with tube placement based on clinical history and otoscopic evaluation in a teriary clinic using accepted standards for placement of tubes for recurrent acute and chronic serous OM in children. Statistical analysis: Student's t-test Fisher's exact test	GERD 1 of 64 + Pepsin result 103 of 509 with OM 1 of 64 without OM Relationship of pepsin with characteristics: Characteristic: Pepsin+, Pepsin- GERD: 7/103, 19/406 Allergy: 3/103, 11/406 Asthma: 7/103, 12/406	Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Yes Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Unknown, based on medical notes Were the reference standard

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding Nemours					results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Orenstein,S.R., Shalaby,T.M., Cohn,J.F., Reflux symptoms in 100 normal infants: diagnostic validity of the infant gastroesophageal reflux questionnaire, Clinical Pediatrics, 35, 607-614, 1996	**Sample size** <u>Normal babies</u> n=100 <u>GORD babies</u> n=35 **Characteristics** <u>Age at time of entry to study in weeks, median (range)</u> Normal babies: 19 (3 to 60) GORD babies: 15 (4 to 56)	**Tests** The I-GERQ questionnaire consisting of items related to demographics and symptoms	**Methods** Ethics approval not reported. Questionnaire completed by a parent of each infant, reading and marking it without assistance.	**Results** <u>Regurgitation</u> >1x/day: normals - 40% GORD infants - 80%, p≤0.001, OR: 2.0 >3x/day: normals - 15% GORD infants - 51%, p≤0.001, OR: 3.4 >5x/day: normals - 6% GORD infants - 31%, p≤0.001, OR: 5.2	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Ref Id 219933 **Country/ies where the study was carried out** USA **Study type** Case-control study **Aim of the study** 1) To identify the prevalence of reflux symptoms in normal infants 2) To characterize the I-GERQ's diagnostic validity for separating nonreferred normal infants from referred infants who have positive diagnostic tests (esophageal biopsy or pH probe) 3) To identify potentially provocative caretaking practices **Study dates** - Normal infants were recruited from those attending the well-baby clinic between January 17 and November 20, 1992 - GORD babies were those referred for evaluation between April 1 1989 and	<u>Sex, % male</u> Normals: 48 GORD: 51 <u>Method of diagnosis</u> Normal: infants attending the well-baby clinic GORD: infants testing positive on either the 24-hour pH probe (pH<4 for> 10% of the total time) or esophageal suction biopsy (basal layer >25% or papillary height >50%) **Inclusion Criteria** <u>Normal babies</u> - Consecutive infants younger than 14 months of age attending the well-baby clinic <u>GORD babies</u> - Infants younger than 14 months of age referred to the gastroenterology division for evaluation for GERD and tested positive on either 24-hour pH probe (pH<4 for> 10% of the total time) or esophageal suction biopsy (basal layer >25% or papillary height >50%) **Exclusion Criteria** <u>Normal babies</u> - Prior reflux evaluation (pH probe, upper gastrointestinal radiography, esophageal biopsy) or treatment (antacid			<u>Regurgitation painful</u> Normals - 12% GORD infants - 63% p≤0.001, OR: 5.3 <u>Feeding refusal</u> Normals - 4% GORD infants - 32% p≤0.001, OR: 8.0 <u>Gags or chokes on feedings</u> Normals - 23% GORD infants - 66% p≤0.001, OR: 2.9 <u>Weight gain problem</u> Normals - 0% GORD infants - 26% p≤0.001, OR: NC <u>Noisy breathing</u> Normals - 34% GORD infants - 63% p≤0.01, OR: 1.9 <u>Apnea</u> ever: normals - 2% GORD infants - 43%, p≤0.001, OR: 21.5 with cyanosis: normals - 0% GORD infants - 16%, p≤0.001, OR: NC with struggling: normals - 1% GORD infants - 23%, p≤0.001, OR: 23 with either: normals - 1% GORD infants - 37%, p≤0.001, OR: 37	Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
September 30 1991 **Source of funding** Supported in part by grants from the National Institute of Health and by United States Public Health Service grant	agent, prokinetic agent) <u>GORD babies</u> - Not reported			<u>Pneumonia ever</u> Normals - 0% GORD infants - 9% p≤0.01, OR: NC <u>Cries ever</u> >normal: normals - 14% GORD infants - 54%, p≤0.001, OR: 3.9 >1hr/day: normals - 17% GORD infants - 54%, p≤0.001, OR: 3.2 >3hr/day: normals - 3% GORD infants - 28%, p≤0.001, OR: 9.3 during/after feed: normals - 14% GORD infants - 80%, p≤0.001, OR: 5.7 <u>Arching</u> Normals - 10% GORD infants - 60% p≤0.001, OR: 6.0	does not match the review question? No, but only one measure of GORD Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? No, control group were not tested Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Peter,C.S., Sprodowski,N., Bohnhorst,B., Silny,J., Poets,C.F., Gastroesophageal reflux and apnea of prematurity: no temporal relationship, Pediatrics, 109, 8-11, 2002 **Ref Id** 238199 **Country/ies where the study was carried out**	**Sample size** 19 **Characteristics** Median gestational age at birth was 30 weeks (24 to 34 weeks) Birthweight was 1150g (660g to 1865g) 5 infants were ventilated at birth 9 receiving treatment for residual lung disease	**Tests** 6-hours of Multiple Intraluminal impednace monitoring, breathing movements via thoracic impedance, ECG, nasal airflow, pulse oximeter saturation.	**Methods** Study design: Prospective cohort Setting: Not stated Ethics: Not stated Positive cases Positive apnoea defined as cessation of breathing effort or airflow for => 4 seconds. Further divided by episodes >20	**Results** Apnoea frequency during reflux 0.19 per minute vs 0.25 per minute in relfux free period. No statistical difference. No correlation between apnoea, bradycardia or desaturation and reflux events.	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced

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Germany **Study type** Prospective cohort study **Aim of the study** Test hypothesis that there is a close temporal relationship between GER and apnoea and reflux usually precedes rather than follows apnoea. **Study dates** Not stated **Source of funding** Young Investigator's Program at Hanover Medical School.	**Inclusion Criteria** <37 weeks gestational age >50% of fluid intake orally Not mechanically ventilated Clinical evidence of apneoa: >2 episodes of apnoea or bradycardia < 100 per minute and/or hypoxemia Ox saturation <=80%) over a 2 hour period of observation **Exclusion Criteria** Conditions resulting in secondary apoena or congenital abnormalities		seconds, heart rate <= 100 beats per minute and SPOs <= 80% Reflux defined as a decrease in impedance starting in the most distal channel and extending over at least 2 channels. Temporal association is witin 20 seconds of events. Statistical analysis: Wilcpxpn's matched pair test to compare reflux with non-reflux periods		bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No, but only one measure of GORD

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Petersen,K.K., Bertelsen,V., Dirdal,M., Funch-Jensen,P., Thommesen,P., The incidence of gastro-oesophageal reflux in children with exogenic and endogenic asthma tested by a new radiological method, Rontgen-Blatter, 42, 527-529, 1989 **Ref Id** 246030 **Country/ies where the study was carried out** Denmark **Study type** Case-control study	**Sample size** 24 cases with asthma 15 controls **Characteristics** Cases: 12 females and 12 males Median age of 8 years (range 1 to 13) Controls 8 females and 7 males Median age of 7 years (range 2 to 10 years) **Inclusion Criteria** <u>Cases</u> Children with asthma <u>Controls</u> Children with no pulmonary	**Tests** Asthma - total serum IgE, number of eosinophils and prick-test. GER tested using barium meal. Test positive if barium ascended more than one vertebra proximal to the gastro-oesophageal junction and at a subsequent test.	**Methods** Study design: Case-control study Setting: Hospital Ethics: No stated Statistical analysis: Chi^2	**Results** Group: Reflux+, Reflux- No asthma: 1, 14 Asthma: 8, 16 Not significant	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without

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Aim of the study Investigate incidence of GER in healthy and asthmatic children. **Study dates** Not stated **Source of funding** Not stated	symptoms or GI symptoms. **Exclusion Criteria** None stated				knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No. Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? No, Barium meal not used to identify GORD Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? Yes Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? No

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No Barium meal used to categorise children as having GERD or not.
Full citation Ruigomez,A., Wallander,M.A., Lundborg,P., Johansson,S., Rodriguez,L.A., Gastroesophageal reflux disease in children and adolescents in primary care, Scandinavian Journal of Gastroenterology, 45, 139-146, 2010 **Ref Id** 238295 **Country/ies where the study was carried out** UK **Study type** Case-control study **Aim of the study** Determine the prevalence and incidence of a	**Sample size** GERD cohort: n = 1700 Control cohort: n = 4977 **Characteristics** GERD cohort: 55% weher adolescent **Inclusion Criteria** <u>GERD cohort</u> Aged 1 to 17 years GERD diagnosis based on Read codes for gastro-oesophageal reflux, reflux esophagitis, esophageal inflammation and heartburn. Did not include non-specific symptoms such as epigastric pain. <u>Control cohort</u> Random selected Aged 1 to 17 years Without diagnosis of GERD	**Tests** GERD based on Read codes. Symptoms based on codes	**Methods** Study design: Cohort study Setting: UK primary care Ethics: Approval to use data granted Data collection: Based on UK primary care database of 2.3 million patients. Statistical analysis: Logistic regression	**Results** Symptom: GERD cohort, control cohort, Adjusted OR, 95% CI Asthma: 431 of 1700, 963 of 4977, 1.0 (0.9 to 1.2) Adjusted for age, sex, year of diagnosis, and number of previous visits to the GP within past year.	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Consecutive in case, random in controls. Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
diagnosis of GERD in children and adolescents in UK primary care, and to assess specific comorbidities that are associated with a diagnosis of GERD, such as congenital and neurological disorders **Study dates** January 2000 to December 2005 **Source of funding** AstraZeneca R&D, Sweden.	**Exclusion Criteria** Pregnant				If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Unclear, based on electronic records Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Unknown Did patients receive the same reference standard? Unknown

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No Based on electronic medical records across a number of GP practices, so variation tests and treatments. Only 15.3% of GERD cohort had a record of a formal diagnostic test being undertaken. None of the children in the control cohort had been tested for GER.
Full citation Sacre,L., Vandenplas,Y., Gastroesophageal reflux associated with respiratory abnormalities during sleep, Journal of Pediatric Gastroenterology and Nutrition, 9, 28-33, 1989 **Ref Id** 219510 **Country/ies where the study was carried out** Belgium **Study type** Case-control study **Aim of the study**	**Sample size** GER group = 60 Control group = 387 of 418 invited **Characteristics** GER group: 6 to 10 weeks old History of emesis for more than 3 weeks or 6 times a day Control group: 6 to 10 weeks old **Inclusion Criteria** Control group: SIDs screening group. GER group Clinical symptoms of GER -	**Tests** GER: 24-pH monitoring. Abnormal pH = >3 standard deviations from age-matched normal GER ranges (separate study) for RI and reflux episodes > 5 minutes. Respiratory function: Polysomnography during sleep for 1 night. Apnoea based on cessation of breating > 15 seconds. Respiratory dsyfunction based on irregular cessation of breathing for 5 to 15 seconds.	**Methods** Study design: Case-control Setting: Not stated Statistical analysis: Chi^2	**Results** Group: No apnoea, Apnoea > 15s, Respiratory dysfunction Control group Normal pH: 378, 2, 5 Abnormal pH: 17, 1, 15 GER group: Before treatment: 35, 1, 24 Difference between groups non-significant at $p < 0.05$	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results

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The purpose of this study were: 1) GER is a possible cause of ALTE 2) Prolonged apnoea can cause GER episode 3) Sleep pattern associated with GER **Study dates** Not stated **Source of funding** Not stated	frequent vomiting abnormal pH result **Exclusion Criteria** Not stated				interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes, Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? No, controls did not

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Salvatore,S., Hauser,B., Vandemaele,K., Novario,R., Vandenplas,Y., Gastroesophageal reflux disease in infants: how much is predictable with questionnaires, pH-metry, endoscopy and histology?, Journal of Pediatric Gastroenterology and Nutrition, 40, 210-215, 2005 **Ref Id** 237858 **Country/ies where the study was carried out** Belgium **Study type** Prospective cohort study **Aim of the study** To identify the prevalence of reflux symptoms in infants and to evaluate the predictive value of a questionnaire and the	**Sample size** n = 200 (100 from well baby clinic, 100 suspected of having GORD) **Characteristics** Age: median age - 4 months, range - 0.5 to 12 months Sex: not reported Method of diagnosis of GORD: All infants had 24-hour pH study, endoscopy was proposed to all infants but only 44 accepted **Inclusion Criteria** <u>Well baby clinic</u> Absence of: - any known disease - any medical/dietary treatment during the 2 weeks preceding the questionnaire - concern by parents or family doctor about the well being of the baby <u>GORD infants</u>	**Tests** Orenstein modified I-GERQ questionnaire.	**Methods** Ethics approval not reported. Questionnaire was filled in by one of the parents, who read and marked it without assistance.	**Results** <u>Pain</u> RI>10, n (%) yes: 5/16 (31) RI<10, n (%) yes: 30/75 (40) p=0.51 <u>Choke</u> RI>10, n (%) yes: 11/21 (52) RI<10, n (%) yes: 46/77 (60) p=0.55 <u>Weight</u> RI>10, n (%) yes: 17/21 (81) RI<10, n (%) yes: 65/78 (83) p=0.8	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
correlation between pH study, histology and clinical score. **Study dates** Not reported **Source of funding** Not reported	- those referred because of GOR symptoms (regurgitation or vomiting with or without distress) **Exclusion Criteria** Not reported				bias? Yes, pain some outcomes are subjective. Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? No, control group not tested. Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Shaw,L., Weatherill,S., Smith,A., Tooth wear in children: an investigation of etiological factors in children with cerebral palsy and gastroesophageal reflux, Journal of Dentistry for Children, 65, 484-486, 1998 **Ref Id** 246205 **Country/ies where the study was carried out** UK **Study type** Prospective cohort study **Aim of the study** Establish the prevalence and disribution of tooth wear in different groups of children and assess the possible influence of reflux, dietary factors and parafunctional activity. **Study dates** Not stated	**Sample size** 51 children: Cerebral palsy with reflux: 12 Cerebal palsy no reflux: 9 Medical condition with reflux: 8 Medical condition no reflux: 22 **Characteristics** **Inclusion Criteria** Children attending clinic **Exclusion Criteria** None stated	**Tests** GER based on medical history, except in cerebal palsy group who underwent 24-hour pH monitoring. Dental erosion based on Wear Index of Smith and Knight. Each tooth scored on a 0 to 4 scale for level of erosion. Mild erosion = no score higher than 1 Moderate = at least one tooth in the dentition scored 2 Sever = at least one tooth in the dentition scored 3 or 4	**Methods** Study design: Prospective cohort Setting: University hospital dental unit Patient recruitment: Children attaending unit. Data collection: Medical records Direct examination Positive and negative cases: GER based on medical records Dental erosion based on direct examination Statistical analysis: Children grouped based on cerebal palsy and GER status Analysis using ANOVA	**Results** Groups: Low erosion %, moderate erosion %, sever erosion % Cerebral palsy with reflux: 25, 25, 50 Cerebal palsy no reflux: 67, 33, 0 Medical condition with reflux: 0, 75, 25 Medical condition no reflux: 77, 17, 5 No statistical difference between groups	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? Unclear Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? Yes, group with CP only. Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Yes, subjective assessment Is there concern that the index test, its conduct, or interpretation differ from the review question? No

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding Not stated					Domain 3 Is the reference standard likely to correctly classify the target condition? Yes, subjective assessment Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Unknown Did patients receive the same reference standard? Unkown Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No Small sample size Not all children had same test for GER Children attending teriary level unit.

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Full citation Siti,Mazliah K., Norzila,M.Z., Deng,C.T., Zulfiqar,A., Azizi,B.H., Prevalence, clinical predictors and diagnosis of gastro-oesophageal reflux in children with persistent respiratory symptoms, Medical Journal of Malaysia, 55, 180-187, 2000 **Ref Id** 238020 **Country/ies where the study was carried out** Malaysia **Study type** Prospective cohort study **Aim of the study** - Determine the prevalence of GOR in children with persistent respiratory symptoms - to identify the clinical predictors of GOR in children with persistent respiratory symptoms - assess the validity of ultrasound, barium oesophahogram and chest radiograph in diagnosing GOR	**Sample size** 44 children **Characteristics** Study demographics: Age (mean, range): 9.1 months (1 to 58 months). Sex: 19 males, 25 females 14 (31.8%) were ex-preterm babies 13 were neurologically impaired (not specified) **Inclusion Criteria** Children referred to Hospital Respiratory Unit due to chronic respiratory symptoms - wheeze recurrent aspiration, recurrent chest infection and stridor. **Exclusion Criteria** None specified	**Tests** Diagnostic tests for GORD: - Ultrasound - Barium oesophagogram - 24-hour pH monitoring Symptoms for GOR: - Recurrent pneumonia - Feeding problem - Recurrent apnoea	**Methods** Design: Cross-sectional study Ethics approval: Not mentioned Setting: Hospital respiratory unit Data collection: All children underwent either ultrasound, barium oesophagogram and pH monitoring. Positive or negative test results: - Positive reflux on ultrasound was defined as presence of ‘to and fro movement of fluid’ into the oesophagus 1 >	**Results** Symptoms: Number (%), number (%) with GOR by pH study - Recurrent pneumonia: 11 (29.5), 6 (13.6) - Feeding problem: 3 (6.8), 2 (4.5) - Recurrent apnoea: 2 (4.5), 2 (4.5) - Persistent cough: sensitivity 51.6%, specificity 53.8% - Vomiting: sensitivity 48.3%, specificity 61.5%	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard

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Study dates Not specified **Source of funding** Not specified			reflux in a ten minute period of scanning. - Barium oesophagogram – reflux twice during 5 minutes of fluoroscopy then reflux was considered. - 24-hour pH Monitoring was based on reflux index (percentage of time when pH was <4) of >14.72% for children age less than 1 year and >5% in children older than 1 year. Statistical analysis: Diagnostic accuracy calculated - sensitivity, specificity, PPV, NPV.		likely to correctly classify the target condition? Yes, but various tests used Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes Did patients receive the same reference standard? No Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Stordal,K., Johannesdottir,G.B., Bentsen,B.S., Sandvik,L., Gastroesophageal reflux disease in children: association between symptoms and pH	**Sample size** 99 children who had a pH study 284 healthy controls matched for age (recuited from Central Population Registry or recruited from schools)	**Tests** Diagnostic tests used: 24-hour pH monitoring performed on day 2 using a Mark-III Digitrapper. Symptoms measured were: - Retrosternal pain/heartburn	**Methods** Study design: 1) Prospective cohort and 2) case-control Ethics approval: Regional ethics committee and informed	**Results** Symptom: Abnormal pH (%, n = 37), Normal pH (%, n = 62), Healthy controls (%, n = 284), adjusted odds ratio (95% CI) for abnormal vs noraml, adjusted odds	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
monitoring, Scandinavian Journal of Gastroenterology, 40, 636-640, 2005 **Ref Id** 238288 **Country/ies where the study was carried out** Norway **Study type** Prospective cohort study **Aim of the study** To validate the items of a questionnaire against results of 24-hour pH monitoring, and to determine the frequency of symptoms associated with GERD in healthy children. **Study dates** Not specified **Source of funding** Not stated	**Characteristics** Variable: abnormal pH (n = 37), normal pH (n = 62), Healthy controls (n = 284) Age (mean, median[years]): 11.5 (11.1), 10.6 (10.4), 10.8 (10.5) Gender (% males): 60, 39, 47 Reflux index (mean, range): 8.8 (5.0-20.0), 2.3 (0.2-4.8), - **Inclusion Criteria** Referred for pH study due to suspected GERD **Exclusion Criteria** Children treated for GERD Children with neuromuscular disease or language problems.	- Abdominal pain - Epigastric pain	consent of parents of children. Setting: Outpatient clinics Data collection: 2-year period, all children referred for pH monitoring. Oesophageal pH-monitoring using a Mark-III Digitrapper. Symptoms collected using 7-item questionnaire completed by parent. Questionnaire was developed by the authors to measure GERD symptoms. Positive and negative cases: Positive cases defined as percentage of time with an oesophageal pH < 4.0. A fractional reflux time of greater than 5% was considered abnormal. Age matched healthy controls identified from population registry and local schools. Statistical analysis: Tests used no specified	ratio (95% CI) for abnormal vs healthy controls - Retrosternal pain/heartburn: 27, 19, 4, 1.48 (0.48, 4.58), 2.9 (0.68, 11.9) - Abdominal pain: 62, 84, 33, 0.38 (0.11, 1.33), 0.96 (0.30, 3.0) - *Epigastric pain: 28, 44, 7, 0.65 (0.23, 1.89), 2.1 (0.58, 7.5)*	enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its

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					interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No, but only one measure of GORD Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? No, control group were not formally tested for GORD Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Stordal,K., Johannesdottir,G.B., Bentsen,B.S., Carlsen,K.C., Sandvik,L., Asthma and overweight are associated with symptoms of gastro-oesophageal reflux, Acta Paediatrica, 95, 1197-1201, 2006 **Ref Id** 236804	**Sample size** Asthma = 872 Control = 264 **Characteristics** Characteristic: case, control Age (mean) years: 10.4, 10.8 Gender % male: 65, 48 **Inclusion Criteria** Asthma cases:	**Tests** GERD: 7-item GERD questionnaire developed and validated by the author. 75% sensitivity and 96% specificity for identifying pH abnormal reflux. 3 or more points on questionnaire considered to have GERD. Asthma: GINA classification of asthma	**Methods** Study design: Case-control study Ethics: Ethical approval gained and informed consent from parents. Setting: Asthma patients from a Paediatric outpatients clinic Controls were age-matched without asthma	**Results** 19.7% of 872 asthma had GERD 8.5% of 264 controls had GERD Asthma+ GERD+ = 172 Asthma+ GERD- = 700 Asthma- GERD+ = 22 Asthma- GERD- = 242 Asthma as a predictor of GERD: unadjusted OR 4.7 (2.4 to 9.5), adjusted OR 4.4 (2.2 to 8.9)	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Country/ies where the study was carried out Norway **Study type** Case-control study **Aim of the study** Assess whether symptoms of gastro-oesophageal reflux were more prevalent in 7 to 16 years old children with asthma than in non-astmatic controls, and whether overweight was associated with GERD symptoms. **Study dates** Not stated **Source of funding** Norwegian Foundation for Health and Rehabilitation AstraZeneca	Physician confirmed asthma Controls: No current asthma **Exclusion Criteria** Neuromusclar disorders and children with language problems.		identified through the Central Population Registry or local schools. Data collection: Positive or negative cases: GERD if 3 or more points on a questionnaire Asthma based on physician diagnosis Statistical analysis:		patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Yes, controls not tested for asthma Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes, but based on survey Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					does not match the review question? No Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No Controls were not formally examined for asthma Presence of GORD based on questionnaire rather than objective diagnostic test.
Full citation Teixeira,B.C., Norton,R.C., Penna,F.J., Camargos,P.A., Lasmar,L.M., Macedo,A.V., Gastroesophageal reflux and asthma in childhood: a study on their relationship using esophageal PH monitoring, Jornal de Pediatria, 83, 535-540, 2007 **Ref Id** 219524 **Country/ies where the**	**Sample size** 69 children **Characteristics** Age, months: 12.4 to 63.1, mean 40.79 (SD 14.59) Sex, male: 62.3% **Inclusion Criteria** Age group - 1 to 5 years Symptoms of asthma before starting treatment Presence of asthma at night,	**Tests** GER test: 24-hours pH monitoring. Children admitted to hospital for test. Asthma test: See inclusion criteria	**Methods** Study design: Cross-sectional survey Setting: Pediatric Pulmonology Outpatient clinic in a teaching hospital Ethics: Not stated Positive or negative GER cases DeMeester score: number of reflux episodes in 24 hours,	**Results** 24 of 41 children with moderate asthma had GER 23 of 28 children with severe asthma had GER p = 0.071	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Consecutive Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? Yes, small sample size

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
study was carried out Brazil **Study type** Prospective cohort study **Aim of the study** Prevalence of GER in children with asthma, and relationship between GER and severity of asthma. **Study dates** Not stated **Source of funding** Not stated	once a wekk or more often Two admissions to hospital due to wheezing in past 6 months or 2 monthly episodes improved by bronchodilators and/or steriods. use of inhaled steriods Positive family history of atopia and/or bronchial asthma Chest x-ray with signs suggesting asthma and ruling out other conditions that mimic asthma Diagnosis for more than 6 months. **Exclusion Criteria** Children with acute exacerbation of asthma		number of episodes > 5 minutes, duration of longest episode, and reflux index. Reflux index = 24-hour pH reflux index of 5%> for children older than 1 year and 10%> for children under 1 year of age. Asthma severity: Moderate - presence of night symptoms one to three times per week. Sever - presence of night symptoms more than three times per week. Data collection: Statistical analysis: Chi^2 with Yates correlation		Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No Domain 4

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Tolia,V., Wuerth,A., Thomas,R., Gastroesophageal reflux disease: Review of presenting symptoms, evaluation, management, and outcome in infants, Digestive Diseases and Sciences, 48, 1723-1729, 2003 **Ref Id** 224945 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study**	**Sample size** 342 infants - 169 controls - 173 cases of GERD **Characteristics** **Inclusion Criteria** Infants aged less than one presenting a children's hospital with symptoms of reflux – spitting/vomiting, choking, gagging, irritability with fussing and arching, feeding problems, ALTE or stridor. **Exclusion Criteria** None stated	**Tests** Diagnostic tests for reflux (details not provided): pH monitoring, Barium study or gastric scintigraphy. Symptoms group into general terms: - Regurgitation - Respiratory - Choking - Irritability	**Methods** Study design: Retrospective case-control study Ethics: Not mentioned Data collection: - Data was extracted from charts. Variables collected included demongraphics, main reported symptoms and results of diagnostic tests. - Symptoms recorded on a 83-point proforma Positive and negative cases: - Positive cases were defined as having at elast one positive diagnostic test. - pH monitoring based on reflux index was =>	**Results** Symptoms: Controls (n = 169), GERD (n = 173) - Regurgitation: 138, 155 - Respiratory: 106, 85 - Choking: 78, 76 - Irritability: 17, 38 - Failure to thrive: 17, 28 - ALTE: 52, 34	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aim to examine course of and outcome of pathological GORD in comparison to controls. **Study dates** January 1994 to April 1997 **Source of funding** Not stated		- Failure to thrive - ALTE	5.0% or Euler and Byrne score was => 50%. - Barium meal was abnormal is one or more of the following noted: reflux, malrotation, hiatal hernia or stricture. - Gastric scintigraphy was based on percentage of ingested formula emptying out of the stomach at the end of 1 hour. Abnormal finding was not defined. Statistical analysis: Symptoms presence assessed using Fisher's exact test		Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? No, some of the test used are no longer thought to be useful Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? No Did patients receive the same reference standard?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					No Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No Retrospective chart review: - Study is liable to provide biased results as not all children had the same tests or had the same information collected. - Study from a secondary care setting
Full citation Uzun,H., Alagoz,D., Okur,M., Dikici,B., Kocabay,K., Senses,D.A., Ozkan,A., Kaya,M., Do gastrointestinal and respiratory signs and symptoms correlate with the severity of gastroesophageal reflux?, BMC Gastroenterology, 12, 22-, 2012 **Ref Id** 246389 **Country/ies where the study was carried out** Turkey **Study type** Prospective cohort study	**Sample size** n = 70 **Characteristics** Age: 2 to 17 years Sex: 57% male, 43% female Method of diagnosis of GERD: 24-hour esophageal pH metry **Inclusion Criteria** Children between the ages of 2 and 17 with suspected GER complaining of heartburn, abdominal pain, recurrent regurgitation, vomiting, failure to thrive, respiratory symptoms such as recurrent respiratory infection, pharyngitis/tonsilitis, otitis, croup, bronchiolitis, persistent cough or wheezing.	**Tests** 24-hour pH metry	**Methods** Ethics approval obtained for the study. A diagnosis of GER was established when reflux index was greater than 4, or DeMeester score higher than 14.7 or pathological reflux considered as at least 1 reflux episode with a pH below 4 in the proximal sensor.	**Results** Vomiting GER +ve: 8 GER -ve: 3 p=0.255 Abdominal pain GER +ve: 9 GER -ve: 4 p= 0.329 Regurgitation GER +ve: 16 GER -ve: 9 p= 0.388 Chronic cough GER +ve: 26 GER -ve: 21 p= 0.857 Non atopic asthma GER +ve: 21 GER -ve: 19 p= 0.676	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aim of the study To determine the prevalence of GER and to evaluate the 24-hour esophageal pH-metry of pediatric patients who had typical and atypical GER symptoms **Study dates** April 2008 to January 2010 **Source of funding** Not reported	**Exclusion Criteria** Not reported				the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Wild,Y.K., Heyman,M.B., Vittinghoff,E., Dalal,D.H., Wojcicki,J.M., Clark,A.L., Rechmann,B., Rechmann,P., Gastroesophageal reflux is not associated with dental erosion in children, Gastroenterology, 141, 1605-1611, 2011 **Ref Id** 237471 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** Investigated the prevalence of dental erosion among children with and without GER symptoms, and whether salivary flow rate or bacterial load contribute to locatio-specific dental erosion.	**Sample size** 84 children recruited 79 Analysed 59 with GER 20 without GER **Characteristics** Characteristics: Cases, Controls Mean age (years): 14.0 (2.4), 11.9 (1.4) Males: 24, 10 **Inclusion Criteria** Children aged 9 to 17 years. Case with symptoms of GER and controls without symptoms **Exclusion Criteria** Children younger than 9 or older than 17 History of systemic disease or a history of conditions potentially affecting oral health or flora, such as diabetes, HIV or heart conditions that require antibiotic prophylaxis	**Tests** GER based on symptoms for longer than 3 months: Abdominal pain, chest pain, heartburn, difficulty swallowing, nausea, vomiting, regurgitation, bitter taste in mouth, burping or belching, choking whilst swallowing, upper abdominal pain after eating. Symptomatic subjects underwent 24 hour pH monitoring Dental examination: Simplified Tooth Wear Index. Based on 0 to 3 (severe) scale for level of erosion on each tooth.	**Methods** Study design: Case-control study Setting: Children's Hospital Ethics: Ethics approval and informed consent. Data collection: Patient medical records pH monitoring Dental examination Statistical analysis: Fisher exact test t-test	**Results** Mean number of erosions per tooth Total teeth: 0.19, 0.11 Location: Upper: 0.15, 0.04* Lower: 0.24, 0.17 Anterior: 0.23, 0.14 Posterior: 0.18, 0.08* Surface: Facial: 0.04, 0.03 Occlusal/incisal: 0.14, 0.05* Lingual: 0.04, 0.05 * statistically signifant p < 0.05 No difference in erosion after adjustment for diet.	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study dates November 2005 and October 2008 **Source of funding** NIH grant Takeda Pharmaceuticals, USA					interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No Unclear if comparison was between childre with pH monitor confirmed GERD or symptomatic GERD.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Costa,A.J.F., Silva,G.A.P., Gouveia,P.A.C., Pereira,FilhoE, Prevalence of pathologic gastroesophageal reflux in regurgitant infants, Jornal de Pediatria, 80, 291-295, 2004 **Ref Id** 237597 **Country/ies where the study was carried out** Brazil **Study type** Prospective cohort study **Aim of the study** To assess the prevalence of pathologic GER in a group of infants treated in a public health service, using clinical criteria based on the Rome II criteria. **Study dates** January to August 2002 **Source of funding** Not reported	**Sample size** n= 798 **Characteristics** Age: 1 to 3 months - 212/797 (27%) 4 to 6 months - 276/797 (35%) 7 to 9 months - 186/797 (23%) 10 to 12 months - 123/797 (15%) Sex: 55.4% male, 44.6% female Method of diagnosis of GERD: Rome II criteria - infants who did not meet the criteria for infant regurgitation (age 1 to 12 months with two or more episodes of regurgitation a day for longer than three weeks, without history of hematemesis, bronchial aspiration, apnea, failure to thrive or abnormal posturing) were classified as suspected cases of pathologic GER. **Inclusion Criteria** - Infants aged 1 to 12 months with a history of regurgitation for at least 3 weeks **Exclusion Criteria** - Severe disease at the time	**Tests** A form was devised for clinical and epidemiological evaluation of symptoms	**Methods** Ethics approval obtained for study. Form completed by caretakers.	**Results** Regurgitation ≥2x/day for longer than 3 weeks yes, n (%) - 89 (100) no, n (%) - 267 (37.7) p value- NR Apnea yes, n (%) - 31 (34.8) no, n (%) - 22 (3.1) p value- 0.001 Failure to thrive yes, n (%) - 27 (30.3) no, n (%) - 28 (3.9) p value- 0.001 Abnormal posturing yes, n (%) - 40 (44.9) no, n (%) - 24 (3.4) p value- 0.001	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	of interview - Diagnosis of bronchial asthma - Infants with neurological disease - Infants who had been submitted to digestive tract surgery or whose guardian could not take care of them during most of the day				likely to correctly classify the target condition? Yes, but based on survey Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No **Other information** Study design: cross sectional study (option not available in drop down list)
Full citation Debley,J.S., Carter,E.R.,	**Sample size** 2797 eligible	**Tests** 26-item ISAAC questionnaire	**Methods** Study design:	**Results** Prevalence of GERD by	**Limitations** Quality assessment based

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Redding,G.J., Prevalence and impact of gastroesophageal reflux in adolescents with asthma: a population-based study, Pediatric Pulmonology, 41, 475-481, 2006 **Ref Id** 238151 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** Hypothesis that: 1) prevalence of GERD symptoms would be higher in children with current asthma symptoms than those without asthma symptoms 2) children with current GERD and Asthma symptoms would report greater morbidity than children with asthma symptoms alone. **Study dates** Not stated	2397 complete survey 1806 included in analysis **Characteristics** Characteristic: undiagnosed current asthma (n = 148), diagnosed current asthma (n = 148), no asthma symptoms (n = 1510) Male (%): 35.5, 47.3, 50.9 **Inclusion Criteria** Attending school. **Exclusion Criteria** None stated	with additional questions in relation to GERD.	Cross-sectional survey Ethics: Approved by ethics commitee Data collection: Questionnaire administered to 13 and 14 year olds in 6 schools in Seattle, USA. Positive or negative cases: Current asthma - Positive response to question: "Have you had wheezing or whistling in the chest in the past 12 months" and as the answer " yes, in the past 12 months" to one of the four video scenairos depicting whezzing. Physician-diagnosed asthma - answered yes to "has a doctor ever told you that you have asthma?" If they answered no then they were classified as having undiagnosed asthma. No current asthma - No to wheezing in past year or video scenairos, and no to physician diagnosed asthma. Symptomatic GERD - answered positive for "in the past month have you had heartburn at least	group: Current asthma: 19.3% (14.9 to 24.2) of 296 had GERD symptoms No asthma symptoms: 2.5% (1.8 to 3.4) of 1510 had GERD symptoms Undiagnosed asthma: 16.9% (10.8 to 23) of 148 had GERD symptoms Diagnosed asthma: 21.6 (14.9 to 28.3) of 148 had GERD symptoms Asthma morbidity: Variable:Children with asthma and weekly GER symptoms (n = 43); Children with asthma and daily GER symptoms (n = 14); Emergency department asthma visits: 2.8 (1.4 to 5.6), 20.9 (4.2 to 104.6) Physician visits for asthma: 1.4 (0.7 to 2.8), 9.4 (2.6 to 34.7) Missed scholl due to asthma: 1.2 (0.6 to 2.4), 12.2 (2.6 to 58) Inhaled medications use > once per week: 2.0 (1.0 to 3.9), 2.6 (0.8 to 8.4)	on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Consecutive Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Yes, based on survey Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? No, based

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding AstraZeneca			once a week?" or in the past month have you had episodes of regurgitation (food or fluid coming up from the stomach) causing bunring in the throat and bad taste at least one a week?. Subjects with positive responses were asked if these symptoms occurred on a daily basis. Also "In tha past 12 months, have you taken antacid medicine?" Statistical analysis: Chi^2 test for differences between groups.		on single queston in survey Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No Based on survey results of symptoms 591 questionnaires excluded as results did not meet criteria for asthma or GERD.
Full citation Guare,R.O., Ferreira,M.C., Leite,M.F., Rodrigues,J.A., Lussi,A., Santos,M.T., Dental erosion and salivary	**Sample size** 46 children cerebral palsy	**Tests** GoORD 24-hour pH monitoring and eosophageal manometry.	**Methods** Study design: Case-control Setting:	**Results** Symptoms: GERD, Controls Regurgitation: 9, 2* Heart burn: 14, 3*	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
flow rate in cerebral palsy individuals with gastroesophageal reflux, Journal of Oral Pathology and Medicine, 41, 367-371, 2012 **Ref Id** 237714 **Country/ies where the study was carried out** Brazil **Study type** Case-control study **Aim of the study** The aim of this study was to evaluate the presence of GERD, dental erosion, and salivary flow rate, in a group of 46 non-institutionalised CP individuals aged 3 to 13 years. **Study dates** Not stated **Source of funding** FAPESP grant 08/00960-6	**Characteristics** Characteristics: GORD, Control N: 20, 26 Age, mean (SD) years: 7.8 (3.8), 10.3 (3.0) Sex male: 14, 11 **Inclusion Criteria** Clinically diagnosed cerebral palsy Aged 3 to 13 years Informed consent signed by guardian **Exclusion Criteria** Previous surgery for saliva control Use drugs that would interfere with saliva secretion for at least 72 hours	Dental erosion Erosion evaluated using Eccles and Jenkins index	Speech therapy service in rehabilitation center Ethics: Ethics committee and parental consent obtained Patient recruitment: Children attending a speech therapy clinic Data collection: pH monitoring Single examiner undertaking dental exam Positive and negative cases: Abnormal = pH values < 4 for 3.4% of the 24 hour period Statistical analysis: Chi^2 used to compare groups	Dental erosion: Grade 0: 2 , 21 Grade 1: 9, 4 Grade 2: 5, 1 Grade 3: 4, 0* Flow rate: 0.54 (SD 0.23), 0.40 (SD 0.33)* * $p < 0.05$	Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? Yes, children with CP only, so recommendation would be restricted to this group Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Yes, a subjective judgement Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Polat,Z., Akgun,O.M., Turan,I., Guven,PolatG, Altun,C., Evaluation of the relationship between dental erosion and scintigraphically detected gastroesophageal reflux in patients with cerebral palsy, Turkish Journal of Medical Sciences, 43, 283-288,	**Sample size** 37 children **Characteristics** 19 males and 18 females Mean age: 12.1 +/- 2.8 years	**Tests** Gord assessed using scintigraphy. Any GERD treatments were stopped 3 days prior to monitoring. Dental examination undertaken by single examiner using index described by O'Sullivan	**Methods** Study design: Case-control study Setting: Specialist centre for children with cerebral palsy Ethics: Ethics approval gained	**Results** Erosion group (n = 21): 78.9% had GERD Control group (n = 16): 21.1% had GERD	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
2013 **Ref Id** 250664 **Country/ies where the study was carried out** Turkey **Study type** Case-control study **Aim of the study** Investigate the association between dental erosion and GERD in patients with cerebral palsy. **Study dates** Not stated **Source of funding** Not stated	**Inclusion Criteria** Children with cerebral palsy **Exclusion Criteria** Tube-fed Sustained uncontrolled seizures History of antireflux treatment Unable to complete scintigraph Guardians did not give consent Undergone dental restorative procedures		Positive or negative cases: Not defined for GORD or dental erosion Statistical analysis: Chi^2		Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Unknown, not defined Could the conduct or interpretation of the index test have introduced bias? No Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Unknown, not defined Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Unknown Did patients receive the same reference standard? Unknown Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Gonda-Domin,M., Lisiecka,K., Rojek,R., Mokrzycka,M., Szymanowicz,J., Glura,B., Dental manifestations of gastroesophageal reflux disease in children, Przeglad Gastroenterologiczny, 8, 180-183, 2013 **Ref Id** 306521 **Country/ies where the**	**Sample size** GERD group: 57 Control group: 57 **Characteristics** <u>GERD cohort</u> Girls: 33/57 (57.9%) Boys: 24/57 (42.1%) **Inclusion Criteria** <u>GERD group</u> - aged 7 to 18 years - GERD diagnoses were established with clinical	**Tests** - GERD diagnoses were established with clinical symptoms esophagogastroduodenoscopy and histological examination - Symptom (dental erosion) based on clinical presentation with degree ranging from a score of 0 to 3, according to the Eccles and Jenkins index. Because of age-related specific conditions such as mixed dentition and typical localisation for tooth erosion in GERD patients, dental examinations were performed	**Methods** Study design: Case-control study Setting: Cases from clinic of Pediatrics, Hematology and Oncology, controls from various schools registered with the Pediatric Dentistry Department Ethics: Not reported Data collection: Source of information not	**Results** <u>Symptom: GERD cohort, control cohort</u> Any dental erosion: 38 out of 57 (66.7%), 15 out 57 (26.3%) ; p <0.0001 Sensitivity (95%CI): 0.67 (0.53 to 0.79)* Specificity (95%CI): 0.74 (0.6 to 0.84)* PPV (95%CI): 0.72 (0.58 to 0.83)* NPV (95%CI): 0.69 (0.56 to 0.8)* LR+(95%CI): 2.53 (1.58 to 4.06)* LR-(95%CI): 0.45 (0.3 to 0.67)*	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
study was carried out Poland **Study type** Case-control study **Aim of the study** To assess the prevalence of dental erosion in a group of 7 to 18 year old children with proven GERD, compared to a healthy control group. **Study dates** Not reported **Source of funding** Not reported	symptoms esophagogastroduodenoscopy and histological examination <u>Control group</u> - randomly chosen subjects of the same age and gender, attending various schools in Szczecin and of patients registered with the Pediatric Dentistry Department of the Pomeranian University of Medicine in Szczecin for routine dental examinations **Exclusion Criteria** Not reported	only on the most susceptible group of teeth: upper incisors and canines.	reported Statistical analysis: The Mann-Whitney U-test was used for comparison between study and control groups. Statistical significance was set at $p<0.05$.	OR (95%CI): 5.6 (2.5 to 12.55)* *Calculated by NCC-WCH technical team based on data reported in the article <u>Severity of teeth erosions</u> GERD cohort: grade I - 113 teeth (73.4%), grade II - 33 teeth (21.4%), grade III - 8 teeth (5.2%) Control cohort: grade I - 34 teeth (64.2%), grade II - 19 teeth (35.8%), grade III - 0 teeth (0%)	included patients do not match the review question? No Domain 2 Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No. Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No Domain 4 Was there an appropriate

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes, but varied between patients Did patients receive the same reference standard? No Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No
Full citation Farahmand,F., Sabbaghian,M., Ghodousi,S., Seddighoraee,N., Abbasi,M., Gastroesophageal reflux disease and tooth erosion: a cross-sectional observational study, Gut and Liver, 7, 278-281, 2013 **Ref Id** 306269 **Country/ies where the study was carried out** Iran **Study type** Case-control study **Aim of the study**	**Sample size** GERD cohort: n=54 Control cohort: n=58 **Characteristics** Male: 58.9%, Female: 41.1% Age: 3 to 12 years (mean: 5.9 years) *The above characteristics are for all 112 children (GERD control + healthy controls) **Inclusion Criteria** <u>GERD cohort</u> GERD diagnoses based on endoscopy, 24 hour pH metry and GERD questionnaire. 3 to 12 years. <u>Control cohort</u> Healthy children who were in	**Tests** - GERD assessed by endoscopy, 24 hour pH metry and GERD questionnaire. - All patients and control group completed a questionnaire to identify other cause of erosion. Some GERD patients and all control group completed a second 35-item Orenstein's modified questionnaire about the presence and frequency of typical GER symptoms (regurgitation, heartburn, dysphagia, and chest pain) and atypical symptoms (hoarseness, cough, wheezing, asthma, etc) with cut-off score >7 points. - Symptom (dental erosion) based on dental evaluation of teeth for the presence, severity, pattern of erosion, stage of dentition, and also a history to determine other potential etiologic factors	**Methods** Study design: Cross-sectional study Setting: Children's Hospital Medical Centre Ethics: Approved by the medical ethics committee Data collection: Questionnaire Statistical analysis: Categorical data were shown as frequency and percent. Chi-square and Fisher's exact tests were performed as appropriate, with p<0.05 considered as statistically significant	**Results** <u>Symptom: GERD cohort, control cohort</u> <u>Dental erosion:</u> 53 out of 54 (98.1%), 11 out of 58 (19%); p<0.0001 Sensitivity (95%CI): 0.98 (0.9 to 1)* Specificity (95%CI): 0.81 (0.69 to 0.9)* PPV (95%CI): 0.83 (0.71 to 0.91)* NPV (95%CI): 0.98 (0.89 to 1)* LR+ (95%CI): 5.18 (3.04 to 8.82)* LR- (95%CI): 0.02 (0 to 0.16)* OR (95%CI): 226.45 (28.16 to 1820.79)* <u>Grade I erosion vs others:</u> 34 out of 53 (64.1%), 8 out of 11 (72.7%) Sensitivity (95%CI): 0.64	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? Yes, children with dental erosion suspected to be caused by diet were excluded Is there concern that the included patients do not match the review question? No Domain 2 Were the index test results

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
To evaluate whether any presence of specific type of erosions could be a key to search for GERD and require referral of the child to gastroenterologist for proper treatments and also if any specific dental care is needed in known GERD patients. **Study dates** January 2009 to January 2010 **Source of funding** Not reported	the same age and at the well baby clinic. Had no known disease or medical/dietary treatment during 2 weeks preceding the study. Parents or family doctors had no concern regarding the well being of the children according to the same GERD questionnaire. Because of ethical reasons, no other investigations were performed in the control group. **Exclusion Criteria** - Children with dental erosion due to diet sources including (carbonated drinks, vinegar, and citrus fruits), medications (vitamin C and some iron preparations), eating disorders (bulimia and anorexia) as well as GERD due to extraintestinal causes such as rising intracranial pressure, urinary tract infection and metabolic disease	responsible for dental erosion. The healthcare professionals who performed the dental exams did not know whether a particular patient had been diagnosed with GERD. Patients were also examined clinically to quantify loss of tooth structure by using Aine tooth wear erosion index.		(0.5 to 0.77)* Specificity (95%CI): 0.27 (0.06 to 0.61)* PPV (95%CI): 0.81 (0.66 to 0.91)* NPV (95%CI): 0.14 (0.03 to 0.35)* LR+ (95%CI): 0.88 (0.58 to 1.33)* LR- (95%CI): 1.31 (0.47 to 3.68)* OR (95%CI): 0.67 (0.16 to 2.83)* <u>Localized vs generalized:</u> 18 out of 53 (34.0%), 5 out of 11 (45.5%) Sensitivity (95%CI): 0.34 (0.22 to 0.48) * Specificity (95%CI): 0.55 (0.23 to 0.83)* PPV (95%CI): 0.78 (0.56 to 0.93)* NPV (95%CI): 0.15 (0.06 to 0.29)* LR+ (95%CI): 0.75 (0.35 to 1.58)* LR- (95%CI): 1.21 (0.68 to 2.15)* OR (95%CI): 0.62 (0.17 to 2.3)* *Calculated by NCC-WCH based on data reported in the article	interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? No. Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No, but only one measure of GORD Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? No,

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					control group did not receive test. Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No - Excluded children where other souces of erosion were identified
Full citation Yuksel,F., Dogan,M., Karatas,D., Yuce,S., Senturk,M., Kulahli,I., Gastroesophageal reflux disease in children with chronic otitis media with effusion, Journal of Craniofacial Surgery, 24, 380-383, 2013 **Ref Id** 257423 **Country/ies where the study was carried out** Turkey **Study type** Prospective cohort study **Aim of the study** To establish the frequency	**Sample size** GERD positive group: n=39 (54.9%) GERD negative group: n=32 (45.1%) **Characteristics** <u>Age in years, mean (SD)</u> GERD positive group - 6.1 (3.5) GERD negative group - 6.5 (2.9) p>0.05 <u>Male gender, n (%)</u> GERD positive group - 15 (40.5%) GERD negative group - 16 (47.1%) p>0.05 <u>Duration of complaints in months, mean (SD)</u> GERD positive group - 25 (19.5)	**Tests** - Patients had undergone a prolonged ambulatory 24 hour esophageal pH monitoring. A decrease in esophageal pH to less than 4 for at least 15 seconds was defined as acid reflux. A reflux index greater than 5% was considered to be reflux positive. Results of gastric scintiscan and 24 hour-pH probe were examined, and at least one positive test resulted in inclusion in the GERD positive group. - Details of how data on symptoms was obtained is not reported (other than 'we recorded age, sex, main complaint and symptoms')	**Methods** Study design: Case-control study Setting: ENT department Ethics: Not reported, informed consent obtained Data collection: Prolonged ambulatory 24 hour esophageal pH monitoring, unclear how data on symptoms was obtained. Statistical analysis: Chi-square test and Fisher's exact test were used to test for the importance between the data. P<0.05 considered to indicate significance.	**Results** <u>Symptom: GERD positive, GERD negative</u> Stridor: 5 out of 39 (12.8%), 2 out of 32 (6.3%), p>0.05 Wheezing: 2 out of 39 (5.1%), 0 out of 32 (0%), p>0.05 Apnea/cyanosis: 2 out of 39 (5.1%), 0 out of 32 (0%), p>0.05 Frequent cough: 21 out of 39 (53.8%), 17 out of 32 (53.1%), p>0.05 Recurrent croup: 4 out of 39 (10.3%), 2 out of 32 (6.3%), p>0.05 Hoarseness: 3 out of 39 (7.7%), 1 out of 32 (3.1%), p>0.05 Feeding complex: 17 out of 39 (43.6%), 11 out of 32 (34.4%), p>0.05 Dysphagia: 8 out of 39 (20.5%), 3 out of 32 (9.4%), p>0.05	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Unknown Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? Yes, a subgroup of children with OME. Domain 2 Were the index test results interpreted without knowledge of the results of

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
of GERD and GERD symptoms as a risk factor in the development of chronic otitis media with effusion in the pediatric age group **Study dates** Not reported **Source of funding** Not reported	GERD negative group - 20.8 (14.5) p>0.05 **Inclusion Criteria** - Children who came to ENT department with the symptoms of hearing loss or aural fullness and diagnosed as otitis media with effusion (OME), which lasted more than 4 months by examination and tympanometry **Exclusion Criteria** - Children who have congenital or acquired abnormalities of upper gastrointestinal tract, neurological disorders, craniofacial anomalies, and allergic rhinitis			Failure to thrive: 7 out of 39 (17.9%), 7 out of 32 (21.9%), p>0.05 Choking/gagging: 5 out of 39 (12.8%), 1 out of 32 (3.1%), p>0.05 Irritability: 8 out of 39 (20.5%), 3 out of 32 (9.4%), p>0.05	the reference standard? Unknown If a threshold was used, was it pre-specified? Yes, based on questionnaire Could the conduct or interpretation of the index test have introduced bias? No. Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No, but only one measure of GORD Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown Did all patients receive a reference standard? Yes Did patients receive the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					same reference standard? No Were all patients included in the analysis? Unknown, but numbers do not match Could the patient flow have introduced bias? No - Children had OME therefore indirect population - Inaccurate reporting of numbers: numbers and percentages often did not match up - Incorrect labeling of GERD positive and GERD negative groups in table of results
Full citation Chen,J.H., Wang,H.Y., Lin,H.H., Wang,C.C., Wang,L.Y., Prevalence and determinants of gastroesophageal reflux symptoms in adolescents, Journal of Gastroenterology and Hepatology, 29, 269-275, 2014 **Ref Id** 306305 **Country/ies where the study was carried out** Taiwan **Study type**	**Sample size** 1828 students attending the four surveyed schools, 1757 (96.1%) returned questionnaires, 12 excluded for incomplete information, therefore 1745 included. **Characteristics** <u>Gender, n (%)</u> Male: 893 (51.1) Female: 852 (48.9) <u>Ethnicity, n (%)</u> Aborigine: 658 (37.7) Han Chinese: 757 (43.4) Bi-ethnic: 300 (17.2) Unknown: 30 (1.7) <u>Cigarette smoking, n (%)</u> Never: 1144 (65.6)	**Tests** - GERD diagnosis based on structured questionnaire. 2 sets of questions were used to assess the presence of GERD symptoms: 1) Have you had a burning feeling occur at the upper stomach near the esophagus and was this burning feeling rising up to the chest, throat, or mouth? This question was used as the surrogate of acid reflux and heartburn. 2) Had you had a painful sensation in the esophagus behind the sternum when swallowing? The frequency of symptom was also obtained from whom positive for any one of the two questions.	**Methods** Study design: Cross sectional study Setting: Public junior schools in east Taiwan Ethics: Approval obtained Data collection: Structured questionnaire Statistical analysis: The chi-square test was used to assess the associations between the presence of GERD and personal attributes. Logistic regression models were performed to evaluate the strength	**Results** <u>Symptom, n(%)</u> Asthmatic symptoms Never: 1268 (72.6) Ever: 477 (27.3) Occurred in the previous year: 302 (17.3) <u>Cumulative prevalence (defined as positive for both questions 1 and/or 2 on the GERD questionnaire coupling with the symptoms occurred at least once per week)</u> Asthmatic symptoms Never: adjusted* OR (95%CI) - 1.00 (reference group) Occurred more than 1	**Limitations** Quality assessment based on QUADAS II (phase 3 use to assess bias) Domain 1 Was a consecutive or random sample of patients enrolled? Consecutive Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unknown Could the selection of patients have introduced bias? No Is there concern that the included patients do not match the review question? No Domain 2

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Prospective cohort study **Aim of the study** To assess the prevalence of GERD, to confirm its association with asthma and to explore its determinants in adolescents. **Study dates** Not reported **Source of funding** Supported by grants from the National Science Council and by grants from Tzu-Chi University	Ever: 599 (34.4) **Inclusion Criteria** - Four public junior high schools with a proportion of aboriginal student ranging from 40% to 60% were selected as surveyed schools - All students attending these schools were invited to participate in the survey **Exclusion Criteria** - Incomplete information association with asthma and GERD	- The presence of asthmatic symptoms was assessed by a validated video questionnaire with verbal instruction published the International Study of Asthma and Allergies in Childhood (ISAAC). Asthma was considered if response to any one of five ISAAC video questions was positive.	of associations between GERD and asthma and food allergy after adjustment of potential confounders.	year before - adjusted* OR (95%CI): 2.43 (1.67 to 3.53) Occurred in the past year - adjusted* OR (95%CI): 3.59 (2.69 to 4.82) <u>3 month prevalence (defined as having GERD symptoms at least once per week during the past 3 months before survey)</u> Never: adjusted* OR (95%CI) - 1.00 (reference group) Occurred more than 1 year before - adjusted* OR (95%CI): 2.26 (1.28 to 3.93) Occurred in the past year - adjusted* OR (95%CI): 5.13 (3.47 to 7.58) *Adjusted for ethnicity, cigarette smoking, food-related allergic symptoms, gender and grade	Were the index test results interpreted without knowledge of the results of the reference standard? Unknown If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Yes, based on questionnaire response only. Is there concern that the index test, its conduct, or interpretation differ from the review question? No Domain 3 Is the reference standard likely to correctly classify the target condition? No, based on questionnaire survey only Were the reference standard results interpreted without knowledge of the results of the index test? Unknown Could the reference standard, its conduct, or its interpretation have introduced bias? No Is there concern that the target condition as defined by the reference standard does not match the review question? No Domain 4 Was there an appropriate interval between index test(s) and reference standard? Unknown

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? No

I.3 What are the risk factors associated with developing GOR/D?

Study details	Participants	Factors	Results	Comments
Full citation Abrahams,P., Burkitt,B.F., Hiatus hernia and gastro-oesophageal reflux in children and adolescents with cerebral palsy, Australian Paediatric Journal, 6, 41-46, 1970 **Ref Id** 244891 **Country/ies where the study was carried out** Australia **Study type** Prospective case-control **Study dates** Not reported **Aim of the study** To attempt to prove that there is a relationship between hiatus hernia or gastroesophageal reflux and cerebral palsy **Source of funding** Not reported	**Cases** Subjects with gastrointestinal symptom complaints **Diagnostic criteria** Complaints referable to the gastro-intestinal tract (such as vomiting and haematemesis). Each patient was examined fluoroscopically, after the ingestion of 4 to 6 ozs of barium, in the supine position and then prone to see whether a hernia or reflux became visible. **Controls** Subjects without gastrointestinal symptom complaints **Inclusion Criteria** - All children with severe physical disability (cerebral palsy) attending The Spastic centre: one group complaining of gastrointestinal symptoms and a second group not complaining of digestive symptoms **Exclusion Criteria** Not reported **Statistical method**	**Factors** - Hiatal hernia (with reflux): each patient was examined fluoroscopically, after the ingestion of 4 to 6 ozs of barium, in the supine position and then prone to see whether a hernia or reflux became visible	**Odds ratios** <u>Odds ratio (unadjusted) for the association between hiatal hernia (with reflux) and gastrointestinal symptoms</u> <u>GI symptoms (Group 1), n/N (%)</u> Hiatal hernia with reflux: 8/16 (50) <u>No GI symptoms (Group 2), n/N (%)</u> Hiatal hernia with reflux: 5/63 (8) OR (95%CI): 11.6 (3.04 to 44.29)	**Limitations** <u>NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies</u> 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - no, all children with cerebral palsy 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - yes 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - no 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - yes **Indirectness** Does the study match the review protocol in terms of;

Study details	Participants	Factors	Results	Comments
	Only numbers (%) have been reported **Demographics** Gestational age in weeks Not reported Birth weight in grams Not reported Race Not reported Male, n/N (%) Not reported Age of subjects (at time of study) 0 to 16 years			Population: No, all children with severe physical disability Outcome: Yes Indirectness: Some **Other information** Setting: The Spastic Centre Sample size: 79 (16 Group 1, 63 Group 2)
Full citation Akinola,E., Rosenkrantz,T.S., Pappagallo,M., McKay,K., Hussain,N., Gastroesophageal reflux in infants < 32 weeks gestational age at birth: lack of relationship to chronic lung disease, American Journal of Perinatology, 21, 57-62, 2004 **Ref Id** 244906 **Country/ies where the study was carried out** USA **Study type**	**Cases** Subjects with GER **Diagnostic criteria** 18 to 24 hour esophageal pH monitoring: infants were identified as positive for GER if there was ≥10% acid reflux with the glucose water feed or ≥5% acid reflux with formula or breast milk **Controls** Subjects without GER as determined by pH probe monitoring	**Factors** - Bronchopulmonary dysplasia defined as oxygen requirement at 28 days of life - Severe chronic lung disease defined as oxygen requirement at 36 weeks postmenstrual age. Postmenstrual age (weeks) was calculated by adding the gestational age at birth (weeks) and postnatal age (weeks).	**Odds ratios** Odds ratio (unadjusted) for the association between bronchopulmonary dysplasia (BPD) and GER GER (Group 1), n/N (%) BPD: 64/87 (74) No GER (Group 2), n/N (%) BPD: 38/50 (76) OR (95% CI): 0.88 (0.39 to 1.97)* * OR (95% CI) calculated by NCC-WCH technical team based on data reported in the article Odds ratio (unadjusted) for the association between severe chronic lung disease (CLD) and GER	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - n/a (retrospective cohort) 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.4 The outcome of interest is adequately measured in study

Study details	Participants	Factors	Results	Comments
Retrospective cohort study **Study dates** January 1996 to December 2000 **Aim of the study** To determine the incidence of gastroesophageal reflux as documented by extended esophageal pH monitoring in symptomatic premature infants and to identify its relationship with chronic lung disease. **Source of funding** Not reported	**Inclusion Criteria** - Infants <32 weeks gestational age admitted to the neonatal intensive care unit identified from a neonatal database of records - Infants with clinical symptoms suggestive of GER and had documented results from extended esophageal pH monitoring; the practice in this centre was to perform extended esophageal pH probe monitoring when infants have clinical symptoms consistent with GER. The most common clinical symptoms included bradycardia, apnea, emesis, poor oral intake and irritability. - Infants who had pH probe monitoring performed also met the following criteria: they were receiving intermittent oral or orogastric feeds; they were not receiving any antireflux or antacid medication at least 48 hours prior to the study; they were able to independently maintain body temperature in an open crib; they were able to maintain upright position in an infant car seat at 45 degrees for the duration of the study. **Exclusion Criteria** - Infants with major congenital anomalies known to be associated with GER		<u>GER (Group 1), n/N (%)</u> CLD: 46/87 (53) <u>No GER (Group 2), n/N (%)</u> CLD: 30/49 (61) OR (95% CI): 0.71 (0.35 to 1.45)* * OR (95% CI) calculated by NCC-WCH technical team based on data reported in the article	participants, sufficient to limit potential bias - yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - no 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - yes **Indirectness** Does the study match the review protocol in terms of; Population: Yes Outcome: Yes Indirectness: None **Other information** - Setting: neonatal intensive care unit - Sample size: 137 - P values were reported for another comparison in the study which hasn't been extracted here - Cases and controls have not been used as defined in the paper but as relevant to this particular review question i.e. cases as those with GORD and controls as those w/o GORD

Study details	Participants	Factors	Results	Comments
	Statistical method Chi-square test for comparison of categorical variables **Demographics** <u>Gestational age in weeks, mean ± SD</u> GER: 27.2 ± 2 NO GER: 27.3 ± 2 <u>Birth weight in grams, mean ± SD</u> GER: 1103 ± 349 NO GER: 999 ± 294 <u>Race, n/N (%)</u> GER: white - 63/87 (72), black - 10/87 (11), Hispanic - 13/87 (15), Other - 0/87 (0) NO GER: white - 37/50 (74), black - 5/50 (10), Hispanic - 4/50 (8), Other - 3/50 (6) <u>Male, n/N (%)</u> GER: 55/87 (63) NO GER: 31/50 (62) <u>Age of subjects (at time of study)</u> Not reported but all subjects were born at <32 weeks gestational age A significance level of less than 0.05 was used for all tests - there were no significant differences for the above characteristics (exact p values not reported)			
Full citation	**Cases**	**Factors**	**Odds ratios**	**Limitations**

Study details	Participants	Factors	Results	Comments
Deurloo,J.A., Smit,B.J., Ekkelkamp,S., Aronson,D.C., Oesophageal atresia in premature infants: an analysis of morbidity and mortality over a period of 20 years, Acta Paediatrica, 93, 394-399, 2004 **Ref Id** 245272 **Country/ies where the study was carried out** The Netherlands **Study type** Retrospective cohort study **Study dates** January 1982 to January 2002 **Aim of the study** To determine the morbidity and mortality of premature infants born with oesophageal atresia and to evaluate historical changes in morbidity and mortality over time. **Source of funding** Not reported	Subjects with GOR **Diagnostic criteria** Diagnosed either by clinical symptoms (n=30) or by 24 hour pH measurement (n=43). **Controls** Subjects without GOR **Inclusion Criteria** Consecutive infants with oesophageal atresia identified from a database of records **Exclusion Criteria** Not reported **Statistical method** Chi-square test **Demographics** <u>Gestational age in weeks, mean (range)</u> Premature: 34.6 (32.0 to 36.9) Term: 39.6 (37.0 to 43.0) <u>Birth weight in grams, mean (range)</u> Premature: 2025 (1100 to 3070) Term: 2968 (1690 to 4160)	- Prematurity: defined as gestational age <37 weeks (very premature birth defined as gestational age <32 weeks)	<u>Odds ratio (unadjusted) for the association between prematurity and GOR</u> <u>GOR (Group 1), n/N (%)</u> Premature: 32/73 (44) <u>No GOR (Group 2), n/N (%)</u> Premature: 44/124 (35) OR (95% CI): 1.42 (0.79 to 2.56)* *OR (95% CI) calculated by NCC-WCH technical team based on data reported in the article	<u>NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies</u> 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - no, infants with oesophageal atresia 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - n/a 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - no 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - yes **Indirectness** Does the study match the review protocol in terms of; Population: no, infants with oesophageal atresia Outcome: Yes Indirectness: Some

Study details	Participants	Factors	Results	Comments
	Race Not reported Male, n/N (%) Premature: 35/55 (64) Term: 68/121 (56)			**Other information** Setting: Paediatric Surgical Centre Sample size: 197
Full citation El-Serag,H.B., Gilger,M., Kuebeler,M., Rabeneck,L., Extraesophageal associations of gastroesophageal reflux disease in children without neurologic defects, Gastroenterology, 121, 1294-1299, 2001 **Ref Id** 245305 **Country/ies where the study was carried out** USA **Study type** Retrospective case-control **Study dates** October 1996 to October 2000 **Aim of the study** To examine association between GERD and several predefined potential	**Cases** Subjects with GERD identified from electronic medical records from children's hospital database **Diagnostic criteria** Based on ICD-9 coding of GERD (530.81, 530.10, 530.11, 530.19, 530.3) **Controls** Subjects without GERD identified from the same computerised database as the cases **Inclusion Criteria** - Cases: children with coding of GERD - Controls: without GERD **Exclusion Criteria** - Cerebral palsy - Mental retardation - Tracheoeosophageal congenital abnormalities	**Factors** - Cystic fibrosis* - Morbid obesity* - Bronchiectasis with or without collapse* *All of the above were diagnosed according to ICD-9 codes	**Odds ratios** Adjusted odds ratios* (95%CI) for the association between cystic fibrosis and GERD GERD, n/N (%) Cystic fibrosis: 50/1980 (2.53) NO GERD, n/N (%) Cystic fibrosis: 59/7920 (0.74) OR (95%CI): 2.89 (1.97 to 4.25) p<0.0001 Adjusted odds ratios* (95%CI) for the association between morbid obesity and GERD GERD, n/N (%) Morbid obesity: 26/1980 (1.31) NO GERD, n/N (%) Morbid obesity: 56/7920 (0.71) OR (95%CI): 1.90 (1.17 to 3.02) p= 0.0074 Adjusted odds ratios* (95%CI) for the association between bronchiectasis (with or without collapse) and GERD GERD, n/N (%) Bronchiectasis: 19/1980 (0.96) NO GERD, n/N (%)	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - n/a 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - no, based on reliability of coding in medical records 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - no, based on reliability of coding in medical records 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - yes 1.6 The statistical analysis is appropriate for the design of the

Study details	Participants	Factors	Results	Comments
extraesophageal manifestations of GERD **Source of funding** Eisai Inc and Janssen Pharmaceutica	- Congenital esophageal stenosis **Statistical method** Chi square and t-tests for univariate analysis **Demographics** Gestational age in weeks Not reported Birth weight in grams Not reported Race, white vs other, n/N (%) Cases: 998/1980 (60.23) Controls: 3112/7920 (41.18) Male, n/N (%) Cases: 969/1980 (48.94) Controls: 4173/7920 (52.69) Age of subjects (at time of study), mean (SD) 2 to 18 years Cases: 9.16 (4.61) Controls: 8.64 (4.92)		Bronchiectasis: 19/7920 (0.06) OR (95%CI): 2.28 (1.14 to 4.57) p=0.0193 *The above odds ratios were adjusted for age, gender and ethnicity	study, limiting potential for the presentation of invalid results - yes **Indirectness** Does the study match the review protocol in terms of; Population: Yes Outcome: Yes Indirectness: None **Other information** Setting: Children's Hospital Sample size: 1980 cases, 7920 controls
Full citation Elitsur,Y., Dementieva,Y., Elitsur,R., Rewalt,M., Obesity is not a risk factor in children with reflux esophagitis: a retrospective analysis of 738 children, Metabolic Syndrome and Related Disorders, 7, 211-214, 2009	**Cases** Subjects with reflux esophagitis identified from records of those who attended a pediatric gastroenterology clinic for various gastrointestinal symptoms **Diagnostic criteria** Histology - the histological reports	**Factors** - Obesity - BMI status was defined as follows: normal weight - BMI <85th percentile, overweight - BMI between 85th and 95th percentiles, obese - BMI >95th percentile	**Odds ratios** Odds ratio (unadjusted) for the association between overweight/obesity and GERD GERD (Group 1), n/N (%) Overweight/obesity: 237/491 (48) No GERD (Group 2), n/N (%) Overweight/obesity: 108/247 (44)	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the

Study details	Participants	Factors	Results	Comments
Ref Id 238024 **Country/ies where the study was carried out** USA **Study type** Retrospective chart review **Study dates** Not reported **Aim of the study** To assess whether being overweight and/or obesity are risk factors for GERD in children, using histology as the diagnostic tool for this disease **Source of funding** Not reported	were based on assessment of at least 3 biopsies obtained from the distal esophagus **Controls** Subjects without reflux esophagitis **Inclusion Criteria** - Children who attended the pediatric gastroenterology clinic for various gastroenterology symptoms **Exclusion Criteria** - Patients less than 2 years of age - Children diagnosed with specific diseases associated with abnormal motility i.e. various neuromuscular diseases, metabolic diseases etc - Those with eosinophilic esophagitis, celiac disease, chronic respiratory illness (asthma) and inflammatory bowel disease - Patients using antiacid (histamine receptor 2 blockers, proton pump inhibitors) and/or antimotility medications within 1 month prior to the procedure **Statistical method** Nonparametric Wilcoxon sum-rank test		OR (95% CI): 1.2 (0.88 to 1.63)* *OR (95% CI) calculated by NCC-WCH technical team based on data reported in the article	study data adequately represent the sample), sufficient to limit potential bias - n/a 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - no 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - yes **Indirectness** Does the study match the review protocol in terms of; Population: Yes Outcome: Yes Indirectness: None **Other information** Setting: Pediatric gastroenterology clinic Sample size: 738

Study details	Participants	Factors	Results	Comments
	Demographics Gestational age in weeks, mean ± SD Not reported Birth weight in grams, mean ± SD Not reported Race, n/N (%) Not reported Male, n/N (%) Normal weight: 186/393 (47) Overweight: 88/161 (55) Obese: 106/184 (58) Age in years, mean (SD) 10.6 (4.2)			
Full citation Forssell,L., Cnattingius,S., Bottai,M., Lagergren,J., Ekbom,A., Akre,O., Risk of esophagitis among individuals born preterm or small for gestational age, Clinical Gastroenterology and Hepatology, 10, 1369-1375, 2012 **Ref Id** 219966 **Country/ies where the study was carried out** Sweden	**Cases** Subjects with esophagitis **Diagnostic criteria** Cases of endoscopically verified esophagitis were ascertained through the Patient Register by combining the discharge diagnoses for esophagitis and the procedure codes for upper endoscopy. Confirmation of the diagnosis was based on the explicit diagnosis of esophagitis, combined with the described macroscopic findings at endoscopy that were found in the charts.	**Factors** - Prematurity (<37 weeks of gestation)	**Odds ratios** Adjusted odds ratios* (95% CI) for the association between gestational age and risk of esophagitis at different ages At ≤9 years **Gestational age ≤ 32 weeks:** 6.82 (4.65 to 10.03) **Gestational age 33 to 36 weeks:** 1.75 (1.42 to 2.14) **Gestational age 37 to 41 weeks:** 1 (reference) **Gestational age 42+ weeks:** 1.10 (0.91 to 1.32) At 10 to 19 years **Gestational age ≤ 32 weeks:** 2.09	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - n/a 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.4 The outcome of interest is adequately measured in study

Study details	Participants	Factors	Results	Comments
Study type Retrospective case-control study **Study dates** Data collected between 1973 and 2007 **Aim of the study** To investigate the association between preterm or small for gestational age birth and risk of esophagitis early in life **Source of funding** Not reported	**Controls** For each case, 5 control subjects were identified. Controls were subjects among singleton births without known malformations at the time of discharge from neonatal care using the Medical Birth Register. Control subjects were selected in a random fashion matched for sex, year of birth, and country of birth. **Inclusion Criteria** - Individuals with endoscopically verified esophagitis from 1973 to 2007 (identified from the Swedish birth register and the Swedish patient register) **Exclusion Criteria** - Children born as twins - Children who had any kind of congenital malformation recorded in the Medical Birth Register because any esophagitis among children with malformations potentially may be caused by factors related to the malformation rather than to the studied birth characteristics **Statistical method** Multivariable conditional logistic regression. Adjusted analyses were stratified by age based on a priori		(1.18 to 3.70) **Gestational age 33 to 36 weeks:** 1.41 (1.10 to 1.80) **Gestational age 37 to 41 weeks:** 1 (reference) **Gestational age 42+ weeks:** 1.26 (1.04 to 1.51) *The above odds ratios were adjusted for birth weight for gestational age, maternal age, and birth order	participants, sufficient to limit potential bias - yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - yes **Indirectness** Does the study match the review protocol in terms of; Population: Yes Outcome: Yes Indirectness: None **Other information** - Setting: hospital records from the Swedish Medical Birth Register and the Swedish Patient Register - Sample size: at ≤ 9 years: 1907 cases, 8808 controls; at 10 to 19 years: 1587 cases, 7138 controls - The Swedish Medical Birth Register was linked with the Swedish Patient register to provide a database for this nationwide case-control study, nested within a cohort of all births in Sweden since 1973. Individual linkages were performed on the

Study details	Participants	Factors	Results	Comments
	hypothesis that the effect of preterm birth might be stronger among those diagnosed at a younger age. **Demographics** Gestational age in weeks Presented in article for all subjects which includes adults (therefore not extracted) Birth weight Presented in article for all subjects which includes adults (therefore not extracted) Race Not reported Male Presented in article for all subjects which includes adults (therefore not extracted) Age (at diagnosis of esophagitis) in years, n (%) 0 to 4: 7240 (17.7) 5 to 9: 3273 (8) 10 to 14: 3565 (8.7) 15 to 19: 5578 (13.7) * The remaining 51.9% of subjects diagnosed were over the age of 19			basis of personal identity number, a unique individual identifier referred to in all hospital records and official registries in Sweden.

Study details	Participants	Factors	Results	Comments
Full citation Fuloria,M., Hiatt,D., Dillard,R.G., O'Shea,T.M., Gastroesophageal reflux in very low birth weight infants: association with chronic lung disease and outcomes through 1 year of age, Journal of Perinatology, 20, 235-239, 2000 **Ref Id** 237926 **Country/ies where the study was carried out** USA **Study type** Retrospective case-control study **Study dates** January 1985 to May 1995 **Aim of the study** To analyse the association between chronic lung disease and clinically diagnosed gastroesophageal reflux in very low birth weight infants and	**Cases** Subjects with GER **Diagnostic criteria** GER was defined as either treatment with anti-reflux medications (metaclopramide, bethanecol, cisparide, cimetidine or ranitidine) or a positive test for GER. Tests for GER included esophageal pH probe, upper gastrointestinal contrast studies and microscopic examination of tracheal aspirates for lipid laden macrophages. (Tests for GER were performed and treatment was initiated at the discretion of the attending neonatologist. Typically, a trial of anti-reflux medications was begun in the presence of the following symptoms: back arching or irritability during or soon after feedings, growth failure attributed to excessive regurgitation of feedings, recurrent aspiration pneumonitis, worsening apnea as volume of feeding was increased, apnea occurring predominantly after feedings, apnea in infants with a postconceptual age of >36 weeks or a positive test for GER). **Controls**	**Factors** - Chronic lung disease: defined as the need for supplemental oxygen at 36 weeks postconceptional age. Severity of chronic lung disease was indicated using 2 measures: the number of days the infant required supplemental oxygen and the type of abnormality on the infant's chest radiograph. - Cerebral palsy: diagnosis of cerebral palsy was made only if a pediatrician and pediatric physical therapist agreed on the presence of abnormal control of movement and posture	**Odds ratios** <u>Adjusted odds ratio* (95%CI) for the association between chronic lung disease (CLD) and GER</u> OR (95%CI): 2.1 (1.1 to 3.5) *The above odds ratio was adjusted for gestational age, gender, race, days on assisted ventilation and days of hospitalisation <u>Unadjusted odds ratio (95%CI) for the association between cerebral palsy and GER</u> <u>CLD with GER (Group 1), n/N (%)</u> Cerebral palsy: 15/111 (14) <u>CLD without GER (Group 2), n/N (%)</u> Cerebral palsy: 31/235 (13) OR (95%CI): 1.03 (0.53 to 1.99)** **OR (95% CI) calculated by NCC-WCH technical team based on data reported in the article	**Limitations** <u>NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies</u> 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - no, very low birth weight premature infants for CLD comparison, very low birth infants with CLD for cerebral palsy comparison 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - n/a 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - yes for CLD, no for cerebral palsy 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results -

Study details	Participants	Factors	Results	Comments
between GER and outcomes (eg: cerebral palsy) at 1 year adjusted age **Source of funding** Not reported	Subjects without GER **Inclusion Criteria** - Very low birth weight infants (≤1500g) with chronic lung disease cared for in either of two level 3 nurseries who survived to 1 year of age identified from a computerised database of records from all admissions to the nurseries. (For the chronic lung disease risk factor, these infants were compared to very low birth infants (≤1500g) without chronic lung disease, who were born closest in time to, and with a gestational age within 1 week of the infant with chronic lung disease) **Exclusion Criteria** - Those for which follow-up information at 1 year corrected age was not available **Statistical method** Logistic regression models. Assessment of confounding - details not reported but seems as though factors with a p value <0.1 on the univariate analyses were adjusted for. **Demographics** Gestational age in weeks, median (range)			yes **Indirectness** Does the study match the review protocol in terms of; Population: No, very low birth weight premature infants for CLD comparison, very low birth infants with CLD for cerebral palsy comparison Outcome: Yes Indirectness: Some **Other information** - Setting: Infants cared for in either of two level 3 nurseries (Brenner Children's Hospital and Forsyth Medical Centre) which together are the sole providers of neonatal intensive care - Sample size: 375 with CLD, 345 without CLD - Cases and controls have not been used as defined in the paper (CLD vs no CLD) but as relevant to this particular review question i.e. cases as those with GORD and controls as those w/o GORD

Study details	Participants	Factors	Results	Comments
	GER: 27 (24 to 31) NO GER: 28 (24 to 31) p=0.07 Birth weight in grams, median (range) GER: 935 (631 to 1439) NO GER: 963 (635 to 1400) p=0.4 Race -non-white, n/N (%) GER: 48/160 (30) NO GER: 240/559 (43) p=0.004 Male, n/N (%) GER: 99/160 (62) NO GER: 263/559 (47) p=0.001			
Full citation Koebnick,C., Getahun,D., Smith,N., Porter,A.H., Der-Sarkissian,J.K., Jacobsen,S.J., Extreme childhood obesity is associated with increased risk for gastroesophageal reflux disease in a large population-based study, International Journal of Pediatric Obesity, 6, e257-e263, 2011 **Ref Id** 219477 **Country/ies where the study was carried out** USA	**Cases** Subjects with GERD identified from electronic medical records **Diagnostic criteria** International Classification of Disease codes (ICD-9 code 530.81). GERD diagnosis was validated in a random subsample of about 5% of cases (n=480) by confirming diagnosis codes for GERD from physician's notes in the electronic medical record. **Controls** Subjects without GERD	**Factors** - BMI (calculated as weight divided by square of the height based on data from electronic medical charts) - Overweight and obesity was defined based on the sex-specific BMI for age growth charts developed by the CDC and WHO definitions for overweight and obesity in adults - Normal weight: BMI for age ≥5th and <85th percentile - Overweight: BMI for age ≥85th percentile or a BMI ≥25kg/m² - Moderately obese: BMI for age ≥95th percentile or a BMI	**Odds ratios** Adjusted odds ratios* (95% CI) for the association between weight class and GERD At 2 to 5 years **Normal weight:** 1 (reference) **Overweight:** 0.95 (0.85 to 1.07) **Moderate obese:** 0.92 (0.80 to 1.06) **Extreme obese:** 1.26 (0.95 to 1.68) At 6 to 11 years **Normal weight:** 1 (reference) **Overweight:** 0.99 (0.87 to 1.12) **Moderate obese:** 1.16 (1.02 to 1.32) **Extreme obese:** 1.32 (1.13 to	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - n/a cross-sectional study 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.4 The outcome of interest is adequately measured in study

Study details	Participants	Factors	Results	Comments
Study type Retrospective cross sectional study **Study dates** 2007 to 2008 **Aim of the study** To investigate the association between BMI and GERD in a population based cross sectional study of more than 690000 racially/ethnically diverse children enrolled in an integrated prepaid health plan **Source of funding** Kaiser Permanente Direct Community Benefit Funds	**Inclusion Criteria** - Subjects enrolled in a prepaid health plan aged 2 to 19 years - At least one valid body weight and height available in the electronic health record **Exclusion Criteria** - Pregnant - Children below normal weight **Statistical method** Multiple logistic regression models **Demographics** <u>Gestational age in weeks</u> Not reported <u>Birth weight</u> Not reported <u>Race, %</u> Non-Hispanic white - normal 28.1; overweight 22.6; moderately obese 17.9; extremely obese 14.8 Hispanic white - normal 40.8; overweight 48.1; moderately obese 54.0; extremely obese 55.4 Black - normal 7.5; overweight 7.8; moderately obese 7.4; extremely obese 9.9 Asian or Pacific Islander - normal 7.8; overweight 5.6; moderately obese 4.9; extremely obese 3.7	≥30kg/m² - Extremely obese: BMI for age ≥1.2 x 95th percentile or a BMI ≥35kg/m²	1.56) <u>At 12 to 19 years</u> **Normal weight:** 1 (reference) **Overweight:** 1.08 (1.01 to 1.15) **Moderate obese:** 1.16 (1.07 to 1.25) **Extreme obese:** 1.40 (1.28 to 1.52) *The above odds ratios were adjusted for sex, race and age within each age group	participants, sufficient to limit potential bias - yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - yes **Indirectness** Does the study match the review protocol in terms of; Population: Yes Outcome: Yes Indirectness: None **Other information** Setting: subjects received their care in medical offices and hospitals Sample size = 690321

Study details	Participants	Factors	Results	Comments
	Others - normal 3.4; overweight 3.2; moderately obese 4.0; extremely obese 3.7 Unknown - normal 12.4; overweight 12.6; moderately obese 11.8; extremely obese 12.6 Male, % Normal 48.6, overweight 48.9, moderately obese 56.3, extremely obese 57.1 Age in years, n (%) 2 to 19 years			
Full citation Kohelet,D., Boaz,M., Serour,F., Cohen-Adad,N., Arbel,E., Gorenstein,A., Esophageal pH study and symptomatology of gastroesophageal reflux in newborn infants, American Journal of Perinatology, 21, 85-91, 2004 **Ref Id** 236928 **Country/ies where the study was carried out** Israel **Study type** Retrospective cohort study **Study dates** January 1995 and 1999	**Cases** Infants diagnosed with GER. **Diagnostic criteria** 24-hour distal esophageal pH monitoring. Reflux was considered pathologic if the proportion of total time with pH <4 during a 24-hour period exceeded 4%. **Controls** Infants without GER. **Inclusion Criteria** Infants born at the Edith Wolfson Medical Centre between January 1995 and 1999 who underwent 24-hour distal esophageal pH monitoring. The indications for pH study in these infants were one or	**Factors** - Prematurity: 25 to 36 weeks of gestation	**Odds ratios** Odds ratio (unadjusted) for the association between prematurity and presence of GER GER, n/N (%) Premature: 18/62 (29) NO GER, n/N (%) Premature: 27/72 (38) OR (95% CI): 0.68 (0.33 to 1.41)* * OR (95% CI) calculated by NCC-WCH technical team based on data reported in the article	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - n/a 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the

Study details	Participants	Factors	Results	Comments
Aim of the study To assess the association between gestational age and esophageal pH monitoring variables in infants investigated for persistent symptomatology attributable to GER **Source of funding** Not reported	more persistent signs suggestive of GER - the signs included persistent episodes of apnea, bradycardia, cyanosis, vomiting and regurgitation. **Exclusion Criteria** Not reported **Statistical method** Chi square test **Demographics** <u>Gestational age in weeks, mean ± SD</u> Group 1 (preterm infants): 30.8 ± 3.3 Group 2 (term infants): 39.4 ± 1.4 p<0.0001 <u>Birth weight in grams, mean ± SD</u> Group 1 (preterm infants): 1626 ± 741 Group 2 (term infants): 3295 ± 490 p<0.0001 <u>Race</u> Not reported <u>Male, n/N (%)</u> Group 1 (preterm infants): 30/45 (67) Group 2 (term infants): 40/89 (45)			prognostic factor of interest - no 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - yes **Indirectness** Does the study match the review protocol in terms of; Population: Yes Outcome: Yes Indirectness: None **Other information** - Setting: Infants were born at the Edith Wolfson Medical Centre - Sample size: 134 - This was a retrospective cohort study comparing preterm against term infants. However for the purpose of this review question, cases have been defined as those with GER and controls those without GER - P values were reported for another comparison in the study which hasn't been extracted here
Full citation	**Cases** Preterm infants with symptoms	**Factors** Chronic lung disease-	**Odds ratios** <u>Adjusted odds ratios* (95% CI) for</u>	**Limitations** <u>NICE guidelines manual 2012:</u>

Study details	Participants	Factors	Results	Comments
Mezzacappa,M.A., Rosa,A.C., Clinical predictors of abnormal esophageal pH monitoring in preterm infants, Arquivos de Gastroenterologia, 45, 234-238, 2008 **Ref Id** 237063 **Country/ies where the study was carried out** Brazil **Study type** Retrospective case-control **Study dates** October 1995 to May 2002 **Aim of the study** To identify factors associated with increased esophageal acid exposition in preterm infants during the stay in the neonatal unit **Source of funding** Not reported	suggestive of GERD **Diagnostic criteria** Prolonged distal intra-esophageal pH monitoring; reflux index ≥10% **Controls** Preterms investigated for clinically suspected GERD and hospitalised during the same period of time as the cases but with a reflux index <10%. One control was chosen for each case. **Inclusion Criteria** - Birth weight < 2000g - Gestational age ≤ 37 weeks - Sample selected from among all patients who had undergone prolonged distal intra-esophageal pH monitoring following clinical indication by the medical team. pH studies routinely undertaken in neonates where GERD suspected, except in patients where vomiting and regurgitation were the only symptoms and in pre-term infants with severe neurological impairment **Exclusion Criteria** - Excluded if monitoring undertaken in non-standardised conditions or when technical problems were encountered	bronchopulmonary dysplasia	<u>the association between bronchopulmonary dysplasia (BPD) and GERD</u> <u>GERD</u> BPD: 33/87 (38%) <u>NO GERD</u> BPD: 44/87 (51%) OR (95%CI): 0.89 (0.46 to 1.75) p= 0.742 *The above odds ratio has been adjusted for birth weight and postconceptional age at time of pH study	<u>Appendix I: Methodology checklist: prognostic studies</u> 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - unclear, 235 pH studies in 193 infants but results for only 174 subjects presented 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - no, details with regards to how BPD was diagnosed is not reported 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - no, not explained which pH test was selected for inclusion as there seems to be more than one per child (235 pH studies in 193 infants) 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - yes **Indirectness**

Study details	Participants	Factors	Results	Comments
	Statistical method Logistic regression analysis. Assessment of confounding: the stepwise selection criteria was applied, taking into consideration those variables with p<0.25 in the univariate analysis. **Demographics** <u>Gestational age in weeks, mean ± SD</u> GER: 28.9 ± 2.2 NO GER: 29.0 ± 2.5 p=0.839 <u>Birth weight in grams, mean ± SD</u> GER: 1185 ± 290 NO GER: 1050 ± 310 p=0.001 <u>Race</u> Not reported <u>Female, n/N (%)</u> GER: 44/87 NO GER: 32/87 p=0.067 <u>Age of subjects at time of study</u> ≤37 weeks gestational age			Does the study match the review protocol in terms of; Population: Yes Outcome: Yes Indirectness: None **Other information** Setting: Hospital Sample size: 174
Full citation Murray,L.J., McCarron,P., McCorry,R.B., Boreham,C.A., McGartland,C.P., Johnston,B.T., Prevalence of	**Cases** Adolescents (and their parents) from postprimary schools with symptoms of epigastric pain, heartburn and/or acid regurgitation.	**Factors** - Family history - Obesity (BMI was calculated as body weight (kg) divided by the square	**Odds ratios** <u>Adjusted odds ratios* (95% CI) for the association between BMI and epigastric pain</u> **Normal:** 1.00 (reference) **Overweight:** 1.09 (0.49 to 2.40)	**Limitations** <u>NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies</u> 1.1 The study sample represents the population of interest with

Study details	Participants	Factors	Results	Comments
epigastric pain, heartburn and acid regurgitation in adolescents and their parents: evidence for intergenerational association, European Journal of Gastroenterology and Hepatology, 19, 297-303, 2007 **Ref Id** 219867 **Country/ies where the study was carried out** Northern Ireland **Study type** Prospective cross-sectional survey (The Young Hearts 2000 study) **Study dates** September 1999 to February 2001 **Aim of the study** To examine the prevalence and familial clustering of, and risk factors for epigastric pain, heartburn and acid regurgitation in adolescents **Source of funding** Funded by a grant from the Department of Health and Social Services in Northern	**Diagnostic criteria** Both adolescents and their parents completed a questionnaire including the following questions: 1) how often in the last 3 months have you had pain or discomfort in the place shown in the picture? (a diagram was included showing the epigastric area) 2) how often in the last 3 months have you had heartburn? (burning or ache behind the breastbone) 3) how often in the last 3 months have you got a very sour or acid tasting fluid at the back of your throat? **Controls** Subjects without symptoms of epigastric pain, heartburn or acid regurgitation **Inclusion Criteria** - Randomly selected adolescents from postprimary schools. (Schools were stratified by education area board and by selection policy (grammar and nongrammar) and within each stratum, two-stage cluster random sampling was employed. The primary sampling units were 36 schools randomly selected from all postprimary schools in Northern Ireland with probabilities proportional to school size. Secondary units were pupils	of standing height (m). Adolescent BMI was categorised into normal, overweight and obese according to the age-sex specific thresholds of Cole et al).	**Obese:** 0.84 (0.20 to 3.65) *The above odds ratios were adjusted for age, sex, social class, household density (persons per room), smoking, alcohol and passive smoking <u>Adjusted odds ratios* (95% CI) for the association between BMI and heartburn</u> **Normal:** 1.00 (reference) **Overweight:** 1.06 (0.35 to 3.21) **Obese:** 0.84 (0.11 to 6.60) *The above odds ratios were adjusted for age, sex, social class, household density (persons per room), smoking, alcohol and passive smoking <u>Adjusted odds ratios* (95% CI) for the association between BMI and acid regurgitation</u> **Normal:** 1.00 (reference) **Overweight:** 1.64 (0.72 to 3.72) **Obese:** 3.46 (1.24 to 9.69) *The above odds ratios were adjusted for age, sex, social class, household density (persons per room), smoking, alcohol and passive smoking <u>Adjusted odds ratios* (95% CI) for the association between family history of epigastric pain and epigastric pain in the adolescent</u> **Neither mother or father has epigastric pain:** adolescent doesn't have epigastric pain n/N (%): 761/963 (79), adolescent has	regard to key characteristics, sufficient to limit potential bias to the results - yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - n/a 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - yes **Indirectness** Does the study match the review protocol in terms of; Population: Yes Outcome: Yes Indirectness: None **Other information** - Setting: adolescents from postprimary schools

Study details	Participants	Factors	Results	Comments
Ireland	randomly selected from the appropriate age-sex groups within the school). **Exclusion Criteria** - Participants whose parental data did not relate to their natural parent (38 subjects) **Statistical method** Multivariate logistic regression models. Details regarding selection of potential confounders not reported. **Demographics** Gestational age in weeks, mean ± SD Not reported Birth weight in grams, mean ± SD Not reported Race, n/N (%) Not reported Male/Female, n/n Epigastric pain: 491/565 Heartburn: 501/591 Acid regurgitation: 488/582 Age in years 13 to 17		epigastric pain n/N (%): 34/52 (65.4), OR (95% CI): 1.00 (reference) **Either mother or father has epigastric pain:** adolescent doesn't have epigastric pain n/N (%): 189/963 (19.6), adolescent has epigastric pain n/N (%): 14/52 (26.9), OR (95% CI): 1.74 (0.82 to 3.69) **Both mother and father have epigastric pain:** adolescent doesn't have epigastric pain n/N (%): 13/963 (1.3), adolescent has epigastric pain n/N (%): 4/52 (7.7), OR (95% CI): 4.15 (0.78 to 22.2) *The above odds ratios were adjusted for adolescent's age, sex, social class, household density (persons per room), BMI category, alcohol intake and smoking status. Analysis was restricted to children living with both natural parents. Adjusted odds ratios* (95% CI) for the association between family history of heartburn and heartburn in the adolescent **Neither mother or father has heartburn:** adolescent doesn't have heartburn n/N (%): 720/988 (72.9), adolescent has heartburn n/N (%): 13/32 (40.6), OR (95% CI): 1.00 (reference) **Either mother of father has heartburn:** adolescent doesn't have heartburn n/N (%): 226/988 (22.9), adolescent has heartburn n/N (%): 13/32 (40.6), OR (95% CI): 2.47 (0.99 to 6.16) **Both mother and father have**	- Overall sample size: 1133

Study details	Participants	Factors	Results	Comments
			heartburn: adolescent doesn't have heartburn n/N (%): 42/988 (4.3), adolescent has heartburn n/N (%): 6/32 (18.8), OR (95% CI): 5.71 (1.62 to 20.1) *The above odds ratios were adjusted for adolescent's age, sex, social class, household density (persons per room), BMI category, alcohol intake and smoking status. Analysis was restricted to children living with both natural parents. <u>Adjusted odds ratios* (95% CI) for the association between family history of acid regurgitation and acid regurgitation in the adolescent</u> **Neither mother or father has acid regurgitation:** adolescent doesn't have acid regurgitation n/N (%): 808/965 (83.7), adolescent has acid regurgitation n/N (%): 30/49 (61.2), OR (95% CI): 1.00 (reference) **Either mother of father has acid regurgitation:** adolescent doesn't have acid regurgitation n/N (%): 147/965 (15.2), adolescent has acid regurgitation n/N (%): 15/49 (30.6), OR (95% CI): 2.54 (1.16 to 5.60) **Both mother and father have acid regurgitation:** adolescent doesn't have acid regurgitation n/N (%): 10/965 (1.0), adolescent has acid regurgitation n/N (%): 4/49 (8.2), OR (95% CI): 6.89 (1.32 to 35.7) *The above odds ratios were adjusted for adolescent's age, sex,	

Study details	Participants	Factors	Results	Comments
			social class, household density (persons per room), BMI category, alcohol intake and smoking status. Analysis was restricted to children living with both natural parents.	
Full citation Pashankar,D.S., Corbin,Z., Shah,S.K., Caprio,S., Increased prevalence of gastroesophageal reflux symptoms in obese children evaluated in an academic medical center, Journal of Clinical Gastroenterology, 43, 410-413, 2009 **Ref Id** 237643 **Country/ies where the study was carried out** USA **Study type** Prospective case-control **Study dates** Obese children recruited from November 2005 and September 2006 Non-obese children recruited from April 2006 and September 2006	**Cases** Subjects with a positive reflux symptom score **Diagnostic criteria** All children were interviewed in person using a standard questionnaire (completed by parents if child younger than 10 years). The questionnaire consists of a history of any sickness in the last 2 weeks and 5 symptoms experienced over the last week (vomiting, nausea, heartburn, regurgitation and dysphagia). A score was given for each symptom and a validated total score of 3 or more was considered a positive reflux symptom score. **Controls** Subjects without a positive reflux symptom score **Inclusion Criteria** - Obese children aged 7 to 16 years from the Obesity clinic	**Factors** - Obesity: weight and height were measured by experienced nursing assistants. BMI calculated as weight divided by height^2. Obesity defined as BMI greater than 95th percentile for age and sex on growth charts from the Center for Disease control.	**Odds ratios** Adjusted odds ratio (95%CI) for the association between obesity and a positive reflux symptom score OR (95%CI)*: 7.4 (1.7 to 32.5) P=0.008 *The above odds ratio was adjusted for age, sex, race and caffeine exposure	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - n/a 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - yes

Study details	Participants	Factors	Results	Comments
Aim of the study To test the hypothesis that obese children are at higher risk of having gastroesophageal reflux symptoms compared with nonobese children **Source of funding** Not reported	(obesity defined as BMI greater than 95th percentile for age and sex on the growth charts from the Center for Disease Control - Control children aged 7 to 16 years with BMI between 5th and 95th percentile for age and sex recruited from the primary care clinic and the adolescent clinic (only children coming for immunisations, well-child visits, school screening examinations or counselling were recruited) **Exclusion Criteria** - Children coming for acute care visits - Children with comorbidities that may predispose to GER such as neurologic impairment, esophageal disorders, chronic respiratory illnesses and motility disorders **Statistical method** Logistic regression **Demographics** <u>Age in years</u> Mean (SD) for obese children: 12.8 (2.6) Mean (SD) for control children: 12.3 (3.2) Range: 7 to 16 years P=Not significant			**Indirectness** Does the study match the review protocol in terms of; Population: Yes Outcome: Yes Indirectness: None **Other information** Setting: Obesity clinic (obese children), primary care clinic and adolescent clinic (non-obese children) Sample size: 337 (236 obese, 101 non-obese)

Study details	Participants	Factors	Results	Comments
	Males, n/N (%) Obese children: 107/236 (45) Non-obese children: 46/101 (46) P=Not significant Race, n/N (%) Obese children: White - 84/236 (36), African American - 71/236 (30), Hispanic - 72/236 (31), Other - 9/236 (4) Non-obese children: White - 14/101 (14), African American - 52/101 (51), Hispanic - 32/101 (32), Other - 3/101 (3) P<0.001, <0.001, not significant and not significant respectively for each ethnic group Smoking exposure, n (%) Obese children: 8/236 (3) Non-obese children: 4/101 (4) P=Not significant Antireflux medications, n (%) Obese children: 6/236 (3) Non-obese children: 1/101 (1) P= Not significant *Significance accepted at P<0.05			
Full citation Quitadamo,P., Buonavolonta,R., Miele,E., Masi,P., Coccorullo,P., Staiano,A., Total and abdominal obesity are risk factors for gastroesophageal reflux symptoms in children, Journal of Pediatric Gastroenterology and Nutrition,	**Cases** Subjects with a positive reflux score (score not defined) **Diagnostic criteria** During the clinic visit, children's esophageal symptoms (heartburn, epigastric pain, vomiting and regurgitation, irritability with meals, dysphagia and/or odynophagia,	**Factors** - Overweight/obesity: height, weight, BMI and waist circumference were determined for each participant. Based on the Institute of Medicine definitions, subjects were classified according to BMI as underweight - BMI <5th percentile, normal weight - BMI 5th to 85th percentile, overweight - BMI 85th to 95th percentile and	**Odds ratios** Odds ratio (unadjusted) for the association between overweight/obese and positive reflux score Positive reflux score, n/N (%) Overweight/obese: 29/49 (59) Negative reflux score, n/N (%) Overweight/obese: 30/104 (29)	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the

Study details	Participants	Factors	Results	Comments
55, 72-75, 2012 **Ref Id** 220122 **Country/ies where the study was carried out** Italy **Study type** Prospective cohort **Study dates** June 2009 to December 2009 **Aim of the study** To evaluate the prevalence of GERD symptoms in overweight and obese children in comparison with a general normal weight population and whether the GERD symptoms are associated with waist circumference **Source of funding** Not reported	respiratory symptoms and hematemesis) during the preceding 2 months were recorded using a standardized questionnaire. The severity and frequency of symptoms were classified into different grades based on a scale used in previous studies. A score for each symptom and a total symptom score were calculated. The score for each symptom was calculated by multiplying the severity grade by the frequency grade, with a possible range for each score of 0 to 9. The total symptom score was calculated by adding up the scores for each symptom. **Controls** Subjects without a positive reflux score **Inclusion Criteria** - Consecutive children between 2 and 18 years referred to the Primary Care Center of the Department of Pediatrics for routine well-child visits **Exclusion Criteria** - Symptoms or findings suggestive of physical disease (eg: abnormal physical examination or laboratory findings, constitutional symptoms such as fever or weight loss) - Acute or chronic illnesses that	obese - BMI >95th percentile and according to waist circumference in children with waist circumference <75th percentile, from 75th to 90th percentile and >90th percentile.	OR (95%CI): 3.58 (1.76 to 7.28)	study data adequately represent the sample), sufficient to limit potential bias - yes 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - no, positive reflux score not defined 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - no 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - yes **Indirectness** Does the study match the review protocol in terms of; Population: Yes Outcome: Yes Indirectness: None **Other information** Setting: Primary care centre Sample size: 153

Study details	Participants	Factors	Results	Comments
	may cause gastrointestinal symptoms - History of major abdominal surgery **Statistical method** Fisher exact test, Chi square test **Demographics** Gestational age in weeks, mean ± SD Not reported Birth weight in grams, mean ± SD Not reported Race, n/N (%) Not reported Male, n/N (%) 75/153 (49) Age in years Mean (SD): 8.17 (4.15) Range: 2 to 17.7			
Full citation Ruigomez,A., Wallander,M.A., Lundborg,P., Johansson,S., Rodriguez,L.A., Gastroesophageal reflux disease in children and adolescents in primary care, Scandinavian Journal of Gastroenterology, 45, 139-146, 2010	**Cases** Subjects with a diagnosis of GERD **Diagnostic criteria** GERD diagnoses were identified by Read codes for gastro-oesophageal reflux, reflux esophagitis, esophageal inflammation and heartburn. Non-specific symptoms such as	**Factors** - Congenital esophageal disorders: includes esophageal atresia, stenosis and traqueoesophageal fistula - Hiatus hernia: includes congenital and acquired hiatus and diaphragmatic hernia - Cystic fibrosis	**Odds ratios** Adjusted odds ratios* (95% CI) for the association between various risk factors and GERD Congenital esophageal disorders, n/N (%) GERD SUBJECTS: 8/1700 (0.5) NO GERD SUBJECTS: 5/4977 (0.1) OR (95%CI): 4.3 (1.3 to 14.1)	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent

Study details	Participants	Factors	Results	Comments
Ref Id 238295 **Country/ies where the study was carried out** UK **Study type** Retrospective cohort **Study dates** January 2000 to December 2005 **Aim of the study** To determine the prevalence and incidence of a diagnosis of GERD in children and adolescents in UK primary care, and to assess specific comorbidities that are associated with a diagnosis of GERD, such as congenital and neurological disorders **Source of funding** AstraZeneca R&D, Sweden	epigastric pain to identify cases was not used unless they were recorded alongside reflux symptoms. **Controls** Subjects without a diagnosis of GERD **Inclusion Criteria** <u>GERD cohort*</u> - Aged 1 to 17 years - GERD diagnosis based on Read codes for gastro-oesophageal reflux, reflux esophagitis, esophageal inflammation and heartburn. Did not include non-specific symptoms such as epigastric pain. <u>Control cohort*</u> - Randomly selected from same source population (matched by age and sex) - Aged 1 to 17 years - Without diagnosis of GERD *All subjects were identified from a UK primary care database of records **Exclusion Criteria** - Pregnant adolescents **Statistical method**	- Neurological disabilities: includes cerebral palsy, neurological syndromes with motor component, chromosomal anomalies, congenital central nervous system anomalies, mental retardation and delayed development, central nervous system neoplasm, and neurological disorders due to neoplasm, trauma, encephalitis and extreme prematurity	<u>Hiatus hernia, n/N (%)</u> GERD SUBJECTS: 13/1700 (0.8) NO GERD SUBJECTS: 6/4977 (0.1) OR (95%CI): 7.4 (2.7 to 20.3) <u>Cystic fibrosis, n/N (%)</u> GERD SUBJECTS: 5/1700 (0.3) NO GERD SUBJECTS: 2/4977 (0.04) OR (95%CI): 3.3 (0.6 to 18.1) <u>Neurological disabilities, n/N (%)</u> GERD SUBJECTS: 107/1700 (6.3) NO GERD SUBJECTS: 72/4977 (1.4) OR (95%CI): 3.4 (2.5 to 4.7) *The above odds ratios were adjusted for age, sex, year of diagnosis, visits to primary care physician in the previous year	the sample), sufficient to limit potential bias - n/a 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - no, only 15.3% of GERD cohort had a record of a formal diagnostic test being undertaken and none of the children in the control cohort had been tested for GER 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - yes **Indirectness** Does the study match the review protocol in terms of; Population: Yes Outcome: Yes Indirectness: None **Other information**

Study details	Participants	Factors	Results	Comments
	Logistic regression. Adjusted for various factors but details of why these confounders were chosen is not given. **Demographics** Gestational age in weeks Not reported Birth weight in grams Not reported Race Not reported Male, n/N (%) 857/1700 (50.4) Age of subjects 1 to 17 years			Setting: UK primary care Sample size: 1700 cases, 4977 controls
Full citation Steward,R.J., Johnston,B.T., Boston,V.E., Dodge,J., Role of hiatal hernia in delaying acid clearance, Archives of Disease in Childhood, 68, 662-664, 1993 **Ref Id** 237015 **Country/ies where the study was carried out** Northern Ireland	**Cases** Subjects with oesophagitis **Diagnostic criteria** Endoscopy: oesophagitis was defined by the demonstration of friability, erosions or ulceration of the mucosa **Controls** Subjects without oesophagitis	**Factors** - Hiatal hernia: identified by barium screening, diagnosed by the identification of gastric mucosal folds or a loculus of stomach above the diaphragm	**Odds ratios** Odds ratio (unadjusted) for the association between hiatal hernia and oesophagitis Oesophagitis (Group 1), n/N (%) Hiatal hernia: 12/20 (60) No oesophagitis (Group 2), n/N (%) Hiatal hernia: 25/75 (33) OR (95% CI): 3 (1.09 to 8.28)* * OR (95% CI) calculated by NCC-WCH technical team based on data reported in the article	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - yes 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - yes

Study details	Participants	Factors	Results	Comments
Study type Prospective cohort **Study dates** Not reported **Aim of the study** To prospectively assess the relationship of a hiatal hernia to gastro-oesophageal reflux **Source of funding** Not reported	**Inclusion Criteria** Consecutive children who presented with symptoms of gastroesophageal reflux and in whom it was demonstrated radiologically (vomiting was present in all patients and in some this was associated with failure to thrive, haematemesis or repeated respiratory tract infections) **Exclusion Criteria** All patients in whom an alternative explanation for vomiting was demonstrated, for example urinary tract infection **Statistical method** Chi square test **Demographics** <u>Age of children in months, mean (range)</u> 28 (0.2 to 180) <u>Gestational age in weeks, mean ± SD</u> Not reported <u>Birth weight in grams, mean ± SD</u> Not reported <u>Race, n/N (%)</u> Not reported <u>Male, n/N (%)</u>			1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - no 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - yes **Indirectness** Does the study match the review protocol in terms of; Population: Yes Outcome: Yes Indirectness: None **Other information** Setting: Hospital Sample size: 95

Study details	Participants	Factors	Results	Comments
	Not reported			
Full citation Stordal,K., Johannesdottir,G.B., Bentsen,B.S., Carlsen,K.C., Sandvik,L., Asthma and overweight are associated with symptoms of gastro-oesophageal reflux, Acta Paediatrica, 95, 1197-1201, 2006 **Ref Id** 236804 **Country/ies where the study was carried out** Norway **Study type** Prospective case-control **Study dates** Not reported **Aim of the study** To assess whether symptoms of gastro-oesophageal reflux were more prevalent in 7 to 16 years old children with asthma than in non-asthmatic controls, and whether overweight was associated with GERD symptoms.	**Cases** Subjects with GERD **Diagnostic criteria** 7-item GERD questionnaire developed and validated by the author. GERD if 3 or more points on a questionnaire. A score of 3 or more points (positive symptom score) has a 75% sensitivity and 96% specificity for GERD defined by an abnormal pH monitoring. **Controls** Subjects without GERD **Inclusion Criteria** - Children aged 7 to 16 years attending pediatric outpatient clinics with doctor diagnosed asthma - Age matched schoolchildren without current asthma **Exclusion Criteria** - Neuromuscular disorders and children with language problems **Statistical method**	**Factors** - Overweight: BMI calculated as weight divided by height² and compared to international age-adjusted percentiles. Overweight and obesity were defined as BMI corresponding to an adult BMI above 25 and 30, respectively.	**Odds ratios** Adjusted odds ratio* (95% CI) for association between overweight and positive GERD symptom score OR (95%CI): 1.6 (1.1 to 2.4) p= 0.019 *The above odds ratio was adjusted for age, gender and asthma	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - no, cases were asthmatics 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - n/a 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - no, presence of GORD based on questionnaire rather than objective diagnostic test 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - yes

Study details	Participants	Factors	Results	Comments
Source of funding Norwegian Foundation for Health and Rehabilitation AstraZeneca	Logistic regression analysis. Confounding was defined as changes in effect estimates of more than 25% from unadjusted to adjusted odds ratios. **Demographics** Gestational age in weeks, mean ± SD Not reported Birth weight in grams, mean ± SD Not reported Race, n/N (%) Not reported Male (%) 65% of asthmatics, 48% of non-asthmatics Age in years 7 to 16			**Indirectness** Does the study match the review protocol in terms of; Population: No, asthmatics Outcome: Yes Indirectness: Some **Other information** Setting: Asthma patients from a Paediatric outpatients clinic. Controls were age-matched without asthma identified through the Central Population Registry or local schools. Sample size: 919 (original sample size = 1136, but BMI available for only 919 subjects)
Full citation Halpern,L.M., Jolley,S.G., Johnson,D.G., Gastroesophageal reflux: a significant association with central nervous system disease in children, Journal of Pediatric Surgery, 26, 171-173, 1991 **Ref Id** 245491 **Country/ies where the study**	**Cases** Subjects with GER n=463* *Calculated by NCC-WCH technical team based on data reported in the article **Diagnostic criteria** - Initial evaluation included an extensive history and physical examination, barium oesophagram, upper gastrointestinal series and 18 to 24 hour esophageal pH	**Factors** 1) CNS disease Mental-motor retardation: including cerebral palsy, developmental delay and mental retardation, n=74 Seizure disorder: n=55 Hydrocephalus: n=15 Microcephaly: n=14 Intracerebral hemorrhage: n=11 Cortical blindness: n=3 Abnormal head CT scan only: n=3 Abnormal EEG without seizures: n=2 Porencephalic cyst: n=2 Spastic quadriplegia: n=2	**Odds ratios** **Total population** With GER, n/N (%) CNS disease: 101/463 (21.8)* Without GER, n/N (%) CNS disease: 31/149 (20.8)* OR (95%CI): 1.06 (0.68 to 1.67)* **Patients older than 1 year** With GER, n/N (%) CNS disease: 31/69 (44.9)*	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - yes 1.3 The prognostic factor of interest is adequately measured

Study details	Participants	Factors	Results	Comments
was carried out USA **Study type** Retrospective review **Study dates** Not reported **Aim of the study** To attempt to identify any association between GER and CNS disease in a group of children who were referred to the pediatric surgical service for an evaluation of GER by extended esophageal pH monitoring **Source of funding** Not reported	monitoring - Documentation of GER by an abnormal pH score derived from 18 to 24 hour esophageal pH monitoring **Controls** Subjects without GER n=149* *Calculated by NCC-WCH technical team based on data reported in the article **Inclusion Criteria** Inclusion criteria not explicitly stated however the subjects were: - children studied by the authors and who underwent an evaluation of GER by 18 to 24 hour esophageal pH monitoring The children were referred by their pediatrician to the pediatric surgical service for the detection, quantification, and possible surgical treatment of GER for the following reasons: 1) a continuation of symptoms following a trial of conventional medical antireflux treatment (thickened feedings, reflux board, pharmacological therapy) 2) children with significant complications associated with GER i.e. esophageal stricture, failure to thrive, respiratory symptoms 3) a determination of the	Cerebral dysgenesis: n=2 Meningomyelocele: n=1 Subarachnoid cyst: n=1 Abnormal brainstem auditory evoked potential only: n=1 Multiple CNS diseases: n=60 Syndromes with CNS involvement: n=21	Without GER, n/N (%) CNS disease: 14/57 (24.6)* OR (95%CI): 2.51 (1.16 to 5.4)* **Patients younger than 1 year** With GER, n/N (%) CNS disease: 70/394 (17.8)* Without GER, n/N (%) CNS disease: 17/92 (18.5)* OR (95%CI): 0.95 (0.53 to 1.71)* *The above numbers and ORs (95%CI) were calculated by the NCC-WCH technical team based on data reported in the article	in study participants, sufficient to limit potential bias - yes but a wide range of CNS conditions grouped together 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - no, ORs calculated by NCC-WCH therefore unadjusted 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - yes **Indirectness** Does the study match the review protocol in terms of: Population: Yes Outcome: Yes Indirectness: None **Other information** Setting: 3 institutions; 1) Primary Children's Medical Center/University of Utah Medical Center 2) Children's hospital of Oklahoma 3) Humana Hospital Sunrise - Las Vegas Sample size: 612 (GER: 463, NO GER: 149)

Study details	Participants	Factors	Results	Comments
	contribution of GER, if any, to the child's symptoms; or 4) to follow-up previous medical or surgical antireflux therapy Subjects were obtained from 3 separate institutions*: 1) Primary Children's Medical Center/University of Utah Medical Center 2) Children's hospital of Oklahoma 3) Humana Hospital Sunrise - Las Vegas *Of 704 children reviewed, 613 were selected because they had no previous esophageal, gastric, or major abdominal surgery **Exclusion Criteria** Not reported **Statistical method** The Fisher Exact test was used to compare patient groups and subgroups **Demographics** <u>Age</u> Range: 1 week to 16 years Mean: 15 months <u>Gender, n</u> Boys: 335 Girls: 278			This was a retrospective review comparing subjects with CNS disease to those without. However for the purpose of this review question, cases have been defined as those with GER and controls as those without GER.

Study details	Participants	Factors	Results	Comments
	CNS disease, n 132 (see factors section for breakdown of different disorders)			

I.4 What clinical features can be used to assess the presence and severity of gastro-oesophageal reflux disease in children and young people?

Bibliographic details	Methods	Results	Reviewer comments	Not needed but mandatory
Authors Sherman,P.M., Hassall,E., Fagundes-Neto,U., Gold,B.D., Kato,S., Koletzko,S., Orenstein,S., Rudolph,C., Vakil,N., Vandenplas,Y. **Year of publication** 2009 **Country of publication** USA **Ref Id** 219036 **Sub-type** Systematic review	**Search strategy** Search between January 1980 to December 2007 on Medline, EMBASE and CINAHL. **Inclusion Criteria** Not stated **Exclusion Criteria** Not stated **Statistical method** Modified Delphi technique used: - International consensus group - development of draft statements - systematic review of literature - voting on statements based on results of review	**Results** Round 1 - 62 statements Round 2 - 117 statements Round 3 - 86 statements Round 4 (final) - 59 statements List of signs, symptoms and risk factors statements: - GORD is defined as troublesome symptoms - Symptoms of GORD vary with age - Regurgitation is associated with GORD - Bilious vomiting is not GORD - Regurgitation is not the only criteria for GORD - Symptoms of GORD may be indistinguishable from food allergy - Those with central nervous system impairment, oeosophageal atresia or cystic fibrosis have increased risk of GORD - Heartburn in retrosternal area - Typical reflux syndrome is heartburn with or without regurgitation - Typical reflux syndrome cannot be identified in young children - Epigastric pain in children and adolescents - Sleep disrubance is associated with GORD - Oesophageal complications of GORD are: reflux oesophagitis, memorrhage, stricture, Barret's oesophagus and rarely adenocaricinoma - Histology cannot be used to diagnose GORD - GORD symptoms do not predict severity of mucosal injury. - Extraesophgeal symptoms include:	**Funding** AstraZeneca R&D and Oxford PharmaGenesis Ltd **Quality Items** Based on NICE manual The review addresses an appropriate and clearly focused question that is relevant to the guideline review question: Unclear The review collects the type of studies you consider relevant to the guideline review question: Unclear The literature search is sufficiently rigorous to identify all the relevant studies: Unclear Study quality is assessed and reported: Yes and No An adequate description of the methodology used is included, and the methods used are appropriate to the question: Yes **Other information**	Consecutive recruitment Raw Data Summary Data Diagnostic criteria Reference Test Demographics - Total Cases Controls Cohort population

Bibliographic details	Methods	Results	Reviewer comments	Not needed but mandatory
		Sandifer's syndrome, dental erosion - Asthma, chronic cough, chronic laryngitis, and hoarseness are associated with and may be aggrevated by GORD - In premature infants the link between GORD and apnea and/or bradycardia is not established - No single diagnostic test can prove or exclude extraesophgeal presentations of GORD. Pathway (not based on review results): In young children (0 to 8 years) - Excessive regurgitation - Feeding refusal/anorexia - Unexplained crying - Choking/gagging/coughing - Sleep distrubance - Abdominal pain In other population: Esophageal: - Typical reflux syndrome - reflux and heartburn AND - Reflux oesophagitis - Reflux stricture - Barret's oesophagas - Adenocaricnoma Extraesophageal: Asthma Pulmonary fibrosis Bronchopulmonary dyspaisia Chronic cough Chronic laryngitis Hoarseness Pharyngitis Sinusitis Serious otis media Pathological apnea		

Bibliographic details	Methods	Results	Reviewer comments	Not needed but mandatory
		Bradycardia ALTE		
Authors Vandenplas,Y., Rudolph,C.D., Di,Lorenzo C., Hassall,E., Liptak,G., Mazur,L., Sondheimer,J., Staiano,A., Thomson,M., Veereman-Wauters,G., Wenzl,T.G., North American Society for Pediatric Gastroenterology Hepatology and Nutrition, European Society for Pediatric Gastroenterology Hepatology and Nutrition. **Year of publication** 2009 **Country of publication** USA **Ref Id** 219819 **Sub-type** Systematic review	**Search strategy** Search between March 1999 (date of previous review) and October 2008 using Pubmed and CINAHL. Additional searching of bibliographies of published articles and US NIH website. **Inclusion Criteria** **Exclusion Criteria** Letters, editorials, case reports and reviews. **Statistical method** No statistical reanalysis undertaken Studies evaluated using Oxford Centre for Evidence-based Medicine Levels of Evidence.	**Results** These are the symptoms and signs identified by the consensus process and have varying levels of evidence associated with them. Symptoms: - Recurrent regurgitation with/without vomiting with age - Weight loss or poor weight gain - Irritability in infants - Ruminative behaviour - Heartburn or chest pain - Hematemesis - Dysphagia, odynophagia - Wheezing - Stridor - Cough - Hoarseness Signs: - Reflux oesophagitis - Oesophageal stricture - Barret oesphagus - Laryngeal/pharyngeal inflammation - Recurrent pneumonia - Anemia - Dental erosion - Feeding refusal - Dystonic neck posturing/sandifer syndrome - Apnea spells - ALTE Signs requiring further investigation in children with regurgitation or vomiting - bilious vomiting - Gastrointestinal bleeding - Consistently forceful vomiting - Onset of vomiting after 6 months of life	**Funding** Funding for review was stated. Conflict of interests were listed for each member of committee. **Quality Items** The review addresses an appropriate and clearly focused question that is relevant to the guideline review question: unclear The review collects the type of studies you consider relevant to the guideline review question: Yes The literature search is sufficiently rigorous to identify all the relevant studies: unclear Study quality is assessed and reported: Yes An adequate description of the methodology used is included, and the methods used are appropriate to the question: Yes **Other information**	Consecutive recruitment Raw Data Summary Data Diagnostic criteria Reference Test Demographics - Total Cases Controls Cohort population

Bibliographic details	Methods	Results	Reviewer comments	Not needed but mandatory
		- Failure to thrive - Diarrhea - Fever - Lethargy - Hepatosplenomegly - Bulging fontanelle - Macro/microcephaly - Seizures - Abdominal tenderness - Genetic/metabolic syndrome		
Authors Tolia,V., Vandenplas,Y. **Year of publication** 2009 **Country of publication** Belgium & USA **Ref Id** 220039 **Sub-type** Systematic review	**Search strategy** Search on Pubmed and EMBASE, dates not given. GORD and synonyms AND Extraoesophageal or specific sign or symptom **Inclusion Criteria** Children aged 0 to 18 years Reported on prevalence of GORD and extra-oesophageal symptoms **Exclusion Criteria** Not stated **Statistical method** Standard data extraction undertaken Method of quality evaluation ot specified Meta-analysis undertaken when	**Results** 903 articles identified 18 included in review (15 epidemiological on specific symptoms and 3 intervention studies) - Asthma - 1 study on Ashtma in children with GORD and 5 studies on GORD in children with ashtma. Studies showed a statistical association between asthma and GORD, but not causative pathway. - Pneumonia - 1 study on pneumonia in children with GORD. A statistical association was found. - ALTE - 1 study on ALTE in children with GORD and 4 studies on GORD in children with ALTE or controls. Studies did not find an statistical association. - Bronchiectasis - 1 study. A statistical association was found. - General respriratory symptoms - 2 studies. A statistical association was found. - ENT symptoms - 2 studies . A statistical association was found. - Dental erosion - 2 studies showing higher prevalence of GORD in those with dental erosion compared to controls - Others symptoms and signs often mentioned by no studies identified	**Funding** AstraZeneca R&D **Quality Items** The review addresses an appropriate and clearly focused question that is relevant to the guideline review question: Yes The review collects the type of studies you consider relevant to the guideline review question: Yes The literature search is sufficiently rigorous to identify all the relevant studies: Yes Study quality is assessed and reported: Yes An adequate description of the methodology used is included, and the methods used are appropriate to the question: Yes **Other information**	Consecutive recruitment Raw Data Summary Data Diagnostic criteria Reference Test Demographics - Total Cases Controls Cohort population

Bibliographic details	Methods	Results	Reviewer comments	Not needed but mandatory
	data available, but method no specified			

I.5 What is the effectiveness of a clearly described positional intervention in comparison with no positional management and alternative clearly described positional interventions?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Bhat,R.Y., Rafferty,G.F., Hannam,S., Greenough,A., Acid gastroesophageal reflux in convalescent preterm infants: effect of posture and relationship to apnea, Pediatric Research, 62, 620-623, 2007 **Ref Id** 238170 **Country/ies where the study was carried out** UK **Study type** Randomised controlled trial - crossover **Aim of the study** To investigate the influence of sleeping position on acid reflux and any association with apnea episodes and to determine whether the presence of bronchopulmonary	**Sample size** N=21 **Characteristics** Age Median postmenstrual age: 36.3 weeks (range: 34.6 to 40.7) Gender Not reported Weight Birth weight: 660 to 1614g Underlying medical conditions 12/21 were oxygen dependant and had or subsequently fulfilled the diagnosis of BPD (oxygen dependency beyond 36 weeks postmenstrual age). All were premature infants. Clinical symptoms Not reported **Inclusion criteria** - Infants born at <33 weeks of gestation who were	**Interventions** Prone versus supine positioning. On each day, infants were examined in both the supine and prone position each for 3 hours. The order in which the positions were examined was randomised between babies, and on the following day, the positions were examined in an individual baby in the opposite order. Results obtained from a particular position on the 2 study days were averaged.	**Details** Consent: parental consent obtained Setting: medical research council asthma centre Sample size calculation: recruitment of 21 infants, each studied in both the supine and prone positions, allowed detection of differences between the supine and prone positions equal to at least 1 SD of the measurements with 90% power at the 5% level. Method: - Infants were studied on 2 successive days - On each day, infants were examined in both the supine and prone position each for 3 hours - The order in which the positions were examined was randomised between babies, and on the following day, the positions were examined in an individual baby in the opposite order - Results obtained from a particular position on the 2 study days were averaged - In each position, lower esophageal pH was measured using a pH probe and videopolysomnographic recordings of nasal airflow, chest, and abdominal wall movements were made	**Results** Reduced frequency of overt regurgitation Not reported Reflux* measured using oesophageal pH metry/impedance monitoring ***Reflux index was calculated as the percentage of study time the esophageal pH was <4. An acid reflux index >12% was considered clinically significant** *Overall* Reflux index %, median (range): prone- 0 (0 to 11.4), supine- 3 (0 to 15.4), p=0.002 *BPD infants* Reflux index %, median (range): prone- 1.8 (0 to 11.4), supine- 3 (0 to 15.4), p=0.03 *Non-BPD infants* Reflux index %, median (range): prone- 0 (0 to 6.4), supine- 6.5 (0 to 10), p=0.03	**Limitations** NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials A Selection bias A1 - Was there appropriate randomisation - unclear, method of randomisation not reported A2 - Was there adequate concealment - unclear A3 - Were groups comparable at baseline - yes, crossover trial therefore infants act as their own control for each comparison Level of bias: unclear B Performance bias B1 - Did groups get same level of care - yes B2 - Were participants blinded to treatment allocation- NA B3 - Were individuals administering care blinded to treatment allocation- NA Level of bias: low C Attrition bias C1 - Was follow-up equal for both groups - yes C2 - Were groups comparable for dropout - yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
dysplasia influenced findings **Study dates** Not reported **Source of funding** King's College Hospital Joint Research Committee and the Foundation for the Study of Infant Death	being prepared for discharge: infants with and without BPD **Exclusion criteria** Not reported		- An acid reflux index was calculated which is the percentage of study time the esophageal pH was <4 - An acid reflux index >12% was considered clinically significant Randomisation method: not reported Outcome measures: reflux index (%) - the percentage of the study time the esophageal pH was <4. An acid reflux index >12% was considered clinically significant. Statistical methods: differences between positions were assessed for statistical significance using the paired Wilcoxon rank-sum test or Mann Whitney U test as appropriate.	Resolution of faltering growth Not reported Adverse outcomes Not reported Parent reported reduction in infant distress Not reported Improvement in validated reflux questionnaire Not reported Parent satisfaction with this intervention Not reported	C3 - Were groups comparable for missing data - yes Level of bias: low D Detection bias D1 - Was follow-up appropriate length - yes D2 - Were outcomes defined precisely - yes D3 - Was a valid and reliable method used to assess outcome - yes D4 - Were investigators blinded to intervention - unclear D5 - Were investigators blinded to confounding factors - unclear Level of bias: low Indirectness Does the study match the review protocol in terms of Population: no, BPD infants Intervention: yes Outcomes: yes Indirectness: some - BPD infants **Other information** Type of position (sleeping/resting/feeding) - Authors state sleeping position was examined - The 3 hour study period began after infants had received a feed

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Orenstein,S.R., Whitington,P.F., Positioning for prevention of infant gastroesophageal reflux, Journal of Pediatrics, 103, 534-537, 1983a **Ref Id** 237745 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial- crossover **Aim of the study** To investigate the hypothesis that in babies with gastroesophageal reflux, the prone, head-elevated position might be superior to positioning in an infant seat in the treatment of reflux **Study dates** Not reported	**Sample size** N=15 **Characteristics** Age Range: 2 weeks to 6 months Mean: 2.5 months Gender Not reported Weight Not reported Underlying medical conditions Not reported Clinical symptoms, n/N Vomiting: 10/15 'Spells' (apnea, cyanosis, stiffening, mouthing): 8/15 Respiratory tract (cough, pneumonia, bronchitis, abnormal findings on chest radiograph): 6/15 Irritability, screaming: 6/15 Failure to thrive: 3/15 Hematemesis, stool occult blood: 2/15 Anorexia: 1/15 **Inclusion criteria** - Children younger than 6 months who were referred	**Interventions** Prone head elevated (at 30 to 45 degrees) positioning in harness versus infant seat elevated at 60 degrees. The harness, when pinned to the mattress supports an infant at any angle to which the mattress is elevated, all infants were placed in it prone, with head elevated 30 to 45 degrees from horizontal.	**Details** Consent: parental consent obtained Setting: children's medical center Sample size calculation: not reported Method: - Distal esophageal pH was recorded for at least 12 hours to document gastroesophageal reflux defined as pH <4 for more than 10% of a postprandial period - During this preliminary pH evaluation, routine care and handling were provided by the parents who were given no instructions regarding positioning - The patients' hands were mitted as needed to prevent dislodgement of the probe - Up to 4 apple juice feedings of unspecified volume were given during this period - Each infant had 2 hours in each position after being fed apple juice (identical volumes for each paired trial) - Infants were thoroughly burped just before each trial - Outcomes were pH esophageal monitoring parameters following a 2 hour postprandial feed of apple juice Randomisation method: the infants were placed in either the seat or harness as determined by lottery for the first 2 hour period, and	**Results** Reduced frequency of overt regurgitation Not reported Reflux* measured using oesophageal pH metry/impedance monitoring ***Reflux episodes were defined as pH <4 for more than 10% of a postprandial period during a 12 hour esophageal pH monitoring session** 1. Percent of time with distal esophageal pH <4, mean ± SEM: Infant seat - 37.4 ± 6.2, Prone head-elevated position in harness - 7.9 ± 2.3; p<0.001 2. Number of episodes with pH <4, mean ± SEM: Infant seat - 19.6 ± 3.5, Prone head-elevated position in harness - 5.2 ± 1.1; p<0.001 3. Number of such episodes lasting longer than 5 minutes, mean ± SEM: Infant seat - 1.9 ± 0.6, Prone head-elevated position in harness - 0.6 ± 0.2; p<0.05 4. Duration of the longest episode in each	**Limitations** NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials A Selection bias A1 - Was there appropriate randomisation - yes A2 - Was there adequate concealment - unclear A3 - Were groups comparable at baseline - yes, crossover trial therefore infants act as their own control for each comparison Level of bias: low B Performance bias B1 - Did groups get same level of care - yes B2 - Were participants blinded to treatment allocation- NA B3 - Were individuals administering care blinded to treatment allocation- NA Level of bias: low C Attrition bias C1 - Was follow-up equal for both groups - yes C2 - Were groups comparable for dropout - yes C3 - Were groups comparable for missing data - yes Level of bias: low D Detection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported	to the gastroenterology service for evaluation for gastroesophageal reflux during a five-month period and in whom reflux has been documented by preliminary overnight pH probe evaluation* *Gastroesophageal reflux was defined as pH <4 for more than 10% of a postprandial period during a 12 hour esophageal pH monitoring session **Exclusion criteria** - Not reported		alternately in the 2 devices during successive periods Outcome measures: percent of time with distal esophageal pH <4, number of episodes with pH <4, number of such episodes lasting longer than 5 minutes, duration of the longest episode in each 2 hour postprandial period. Statistical methods: Data for the 2 positions were compared using the student t test for paired observations, the student t test for unpaired observations was used to determine the significance of group mean differences	2 hour postprandial period, mean ± SEM: Infant seat - 13.1 ± 5.0, Prone head-elevated position in harness - 5.0 ± 1.7; p<0.05 Resolution of faltering growth Not reported Adverse outcomes Not reported Parent reported reduction in infant distress Not reported Improvement in validated reflux questionnaire Not reported Parent satisfaction with this intervention Not reported	D1 - Was follow-up appropriate length - yes D2 - Were outcomes defined precisely - yes D3 - Was a valid and reliable method used to assess outcome - yes D4 - Were investigators blinded to intervention - unclear D5 - Were investigators blinded to confounding factors - unclear Level of bias: low Indirectness Does the study match the review protocol in terms of Population: yes Intervention: yes Outcomes: yes Indirectness: None **Other information** Type of position (sleeping/resting/feeding) - Though not explicitly stated, it seems as though sleeping/resting position was examined - Infant was positioned after feed (postprandial study period)
Full citation Tobin,J.M., McCloud,P., Cameron,D.J., Posture	**Sample size** N=24	**Interventions** Eight different positions were being studied: prone, supine, right lateral and left	**Details** Consent: parental consent obtained Setting: paediatric gastroenterology	**Results** Reduced frequency of overt regurgitation Not reported	**Limitations** NICE guidelines manual 2012: Appendix C: Methodology checklist:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and gastro-oesophageal reflux: a case for left lateral positioning, Archives of Disease in Childhood, 76, 254-258, 1997 **Ref Id** 219849 **Country/ies where the study was carried out** Australia **Study type** Randomised controlled trial - crossover **Aim of the study** To evaluate prospectively the effects of position and elevation in young infants with symptomatic gastroesophageal reflux and a reflux index of greater than 5% **Study dates** May 1992 to May 1994 **Source of funding** Helen M Schutt Trust Fund, Truby and	**Characteristics** Age Mean: 2 months Range: >4 days post-delivery and less than 5 months Gender Female: 13/24 Male: 11/24 Weight Not reported Underlying medical conditions Not reported Clinical symptoms, n/N Vomiting: 20/24 Poor feeding: 4/24 Irritability: 11/24 Choking/apnoeic spells: 10/24 Weight concerns: 3/24 **Inclusion criteria** - Infants referred to the Pediatric gastroenterology unit for evaluation of possible gastroesophageal reflux, reflux index >5% - Infants more than 4 days post-delivery and less than 5 months of age, with no previous gastrointestinal surgery (upper age limit	lateral held in a horizontal manner for the first 24 hours then elevated at 30 degrees. Each infant was assigned a set of positions, randomly drawn from the 24 envelope set of all possible permutations, before pH monitoring. This gave each infant a block of 8 segments and 6 hours of pH monitoring in each position. *Elevation was not randomised with the infants receiving the first 4 positions in the horizontal manner on the first day and then the permutation repeated in the elevated position on the second day.	unit Sample size calculation: with α=0.05, power= 0.8 and 'within infant' deviation of 7.5, a sample size of 16 was required to detect an absolute difference of 5% (reflux index) between 2 positions. 4 different positions provide 24 possible permutations so in order to use the full set, the sample size was increased to 24. Method: - 24 infants with symptomatic gastro-oesophageal reflux were studied prospectively with 48 hour pH monitoring - They were randomly assigned to one of the 24 permutations of the 4 positions (supine, prone, right and left lateral) - During the first 24 hours, the infant was held horizontally, and then the permutation was repeated at 30 degrees head elevation, giving a total of 8 segments for each infant - Results were evaluated using analysis of covariance Randomisation method: each infant was assigned a set of positions (for example: prone, supine, right lateral, left lateral, held horizontally during the first 24 hours, then elevated), randomly drawn from the 24 envelope set of all possible permutations, before pH monitoring. This gave each infant a block of 8 segments of six hours.	Reflux* measured using oesophageal pH metry/impedance monitoring ***Reflux episodes were defined as an abrupt fall in intraoesophageal pH to less than 4 for at least 15 seconds** Prone versus supine Reflux index, mean (SEM): prone- 6.72 (1.06), supine- 15.33 (2.33) Prone versus right lateral Reflux index, mean (SEM): prone- 6.72 (1.06), right lateral- 12.02 (1.38) Left lateral versus supine Reflux index, mean (SEM): left lateral- 7.69 (1.03), supine- 15.33 (2.33) Left lateral versus right lateral Reflux index, mean (SEM): left lateral- 7.69 (1.03), right lateral- 12.02 (1.38) Prone versus left lateral Reflux index, mean (SEM): prone: 6.72 (1.06), left lateral- 7.69 (1.03) Resolution of faltering	randomised controlled trials A Selection bias A1 - Was there appropriate randomisation - yes A2 - Was there adequate concealment - yes, envelopes A3 - Were groups comparable at baseline - yes, crossover trial therefore infants act as their own control for each comparison Level of bias: low B Performance bias B1 - Did groups get same level of care - yes B2 - Were participants blinded to treatment allocation- NA B3 - Were individuals administering care blinded to treatment allocation- NA Level of bias: low C Attrition bias C1 - Was follow-up equal for both groups - yes C2 - Were groups comparable for dropout - yes C3 - Were groups comparable for missing data - yes Level of bias: unclear D Detection bias D1 - Was follow-up appropriate length - yes D2 - Were outcomes defined precisely - yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Florence Williams Memorial Trust, ANZ Trustees	chosen because of difficulty in maintaining a mobile infant in position) - Nursing in an open cot and at 30 degrees elevation had to be possible **Exclusion criteria** - Reflux index of less than 5% - Technical reasons - Inadequate diary completion		Outcome measures: reflux index (percentage of time pH was less than 4), number of reflux episodes, number of episodes greater than 5 minutes, duration of longest episode Statistical methods: Reflux activity data were analysed by analysis of covariance. The treatment factors included in the analysis as main effects were position, time of day, degree of elevation and the interaction between position and elevation.	growth Not reported Adverse outcomes Not reported Parent reported reduction in infant distress Not reported Improvement in validated reflux questionnaire Not reported Parent satisfaction with this intervention Not reported	D3 - Was a valid and reliable method used to assess outcome - yes D4 - Were investigators blinded to intervention - unclear D5 - Were investigators blinded to confounding factors - unclear Level of bias: low Indirectness Does the study match the review protocol in terms of Population: yes Intervention: yes Outcomes: yes Indirectness: none **Other information** Type of position (sleeping/resting/feeding) - Not explicitly stated but seems as though sleeping/resting position was examined - Parents were encouraged to leave infants in position as much as possible, to feed only at their scheduled times and to put them back down promptly
Full citation Ewer,A.K., James,M.E., Tobin,J.M., Prone and left lateral positioning	**Sample size** N= 18	**Interventions** Infants were nursed in 3 positions (prone, left lateral and right lateral) for 8 hours in each position	**Details** Consent: parental consent obtained Setting: neonatal intensive care unit	**Results** Reduced frequency of overt regurgitation Not reported	**Limitations** NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
reduce gastro-oesophageal reflux in preterm infants, Archives of Disease in Childhood Fetal and Neonatal Edition, 81, F201-F205, 1999 **Ref Id** 237025 **Country/ies where the study was carried out** UK **Study type** Randomised controlled trial - crossover **Aim of the study** To examine the effect of body position on clinically significant gastroesophageal reflux in preterm infants **Study dates** Not reported **Source of funding** Not reported	**Characteristics** Age 27 days (11 to 73 days) Gender Male: 12/18 Female: 6/18 Weight 945g (480 to 1750g) - birth weight Underlying medical conditions Prematurity Clinical symptoms Excessive regurgitation of feeds, xanthine resistant apnoea, bradycardia **Inclusion criteria** - Preterm delivery (less than 37 weeks of gestation) - More than 7 days old - Receiving full enteral feeds at a minimum of 150ml/kg/day **Exclusion criteria** - Incompletion of study because of clinical deterioration which required discontinuation of feeds		Sample size calculation: not reported Method: - 18 preterm infants with clinically significant GOR (reflux index >5%) were studied prospectively using 24 hour lower oesophageal pH monitoring - Infants were nursed in 3 positions (prone, left and right lateral) for 8 hours in each position, with the order randomly assigned - Data were analysed using analysis of covariance Randomisation method: each infant was randomly assigned by sealed envelope to one of six permutations of the 3 nursing positions (right lateral, left lateral, prone; prone, left lateral, right lateral, etc) and the infant was successively nursed in each of these positions for periods of 8 hours (or as near as possible) during the study Outcome measures: reflux index, number of reflux episodes, episodes greater 5 minutes, duration of longest episode Statistical methods: The reflux parameters in each of the positions were analysed using analysis of covariance. Pairwise comparisons of means were done with the least significant difference method at the 5% level to evaluate the differences between positions.	Reflux* measured using oesophageal pH metry ***Reflux episodes were defined as pH <4 for 15 seconds or longer. Reflux index was defined as the percentage of study time during which lower oesophageal pH was <4.0.** 1. Reflux index %, mean (SEM): prone- 6.3 (1.7) left lateral- 11.0 (2.2), right lateral-29.4 (3.2), p<0.001 2. Number of episodes with pH <4, mean (SEM): prone- 15.4 (2.8), left lateral- 24.6 (3.5), right lateral-41.6 (4.6), p<0.001 3. Number of such episodes longer than 5 minutes, mean (SEM): prone- 1.1 (0.4), left lateral- 1.8 (0.5), right lateral-4.5 (0.8), p=0.002 4. Duration of the longest episode, mean (SEM): prone-8.6 (2.2), left lateral-10.0 (2.4), right lateral-26.0 (3.9), p<0.001 Resolution of faltering growth Not reported Adverse outcomes	A Selection bias A1 - Was there appropriate randomisation - yes A2 - Was there adequate concealment - yes, sealed envelopes A3 - Were groups comparable at baseline - yes, crossover trial therefore infants act as their own control for each comparison Level of bias: low B Performance bias B1 - Did groups get same level of care - yes B2 - Were participants blinded to treatment allocation- NA B3 - Were individuals administering care blinded to treatment allocation- NA Level of bias: low C Attrition bias C1 - Was follow-up equal for both groups - yes C2 - Were groups comparable for dropout - yes C3 - Were groups comparable for missing data - yes Level of bias: low D Detection bias D1 - Was follow-up appropriate length - yes D2 - Were outcomes defined precisely - yes D3 - Was a valid and reliable

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Absence of clinically significant reflux, reflux index less than 5% - Infant not nursed in one of the three positions for clinical reasons - Position documentation was unsatisfactory - Time spent in each position was impossible to calculate accurately			Not reported Parent reported reduction in infant distress Not reported Improvement in validated reflux questionnaire Not reported Parent satisfaction with this intervention Not reported	method used to assess outcome - yes D4 - Were investigators blinded to intervention - unclear D5 - Were investigators blinded to confounding factors - unclear Level of bias: low Indirectness Does the study match the review protocol in terms of Population: yes, (subgroup: preterm infants) Intervention: yes Outcomes: yes Indirectness: none **Other information** Type of position (sleeping/resting/feeding) - Not explictly stated but position was not altered during or immediately after feeds
Full citation Orenstein,S.R., Prone positioning in infant gastroesophageal reflux: is elevation of the head worth the trouble?, Journal of Pediatrics, 117, 184-187, 1990 **Ref Id**	**Sample size** N= 90* *sample size was originally 100 but only 90 were documented to have abnormal reflux - data for these 90 infants has been extracted for this review	**Interventions** Head-elevated* prone positioning versus flat prone** positioning *For the head-elevated prone period, the mattress was inclined 30 degrees and the infants kept in position by use of a cloth harness **For the flat prone period,	**Details** Consent: parental consent obtained Setting: clinical research centre Sample size calculation: the 100 subjects recruited provided the power to detect a difference of 9½ minutes of reflux during the postprandial 2 hours with an α of 0.05 and β of 0.80	**Results** Reduced frequency of overt regurgitation Not reported Reflux* measured using oesophageal pH metry/impedance monitoring ***Reflux episodes were defined as beginning when the pH dropped**	**Limitations** NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials A Selection bias A1 - Was there appropriate randomisation - yes A2 - Was there adequate concealment - unclear A3 - Were groups

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
160681 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial - crossover **Aim of the study** To determine whether head-elevated prone positioning is better than flat prone positioning for infants with gastroesophageal reflux **Study dates** September 1987 to August 1989 **Source of funding** - National Institute of Health - US Public Health Service	**Characteristics** Age Median: 10.5 weeks Range: 4 to 26 weeks Gender Not reported Weight Not reported Underlying medical conditions Not reported Clinical symptoms, n/N Emesis: 56/90 Respiratory (cough, wheeze, infiltrates): 15/90 Stridor, hoarseness: 10/90 Apnea, cyanosis, choke, 'spells': 46/90 Irritability: 37/90 Failure to thrive: 23/90 **Inclusion criteria** - Infants younger than 6 months of age in whom abnormal reflux was suspected clinically: 90/100 subjects were documented to have abnormal reflux on the basis of pH probe* or histologic examination** *Documentation of abnormal reflux by pH	infants were kept prone on a horizontal mattress	Method: - Each infant was transferred to the clinical research center after a pH probe was inserted the evening before the study - Apple juice feedings were then given every 3 to 4 hours until 4.30 AM - At 4.30 AM and 10.30 AM, for reduction of hunger related behaviour, each infant was given a standard volume of his or her regular formula (2ml/cm of height) - At 7.30 AM and 1.30 PM, apple juice feedings were given in the same standard volume and were followed by either of the two study periods of nearly 3 hours in a crossover design - Infants were not handled after being placed in position - Outcomes were pH esophageal monitoring parameters following a 2 hour postprandial feed of apple juice - After removal of the pH probe, all but 3 infants had esophageal suction biopsy to document histologic esophagitis Randomisation method: the order in which the positions were studied in each infant was randomly assigned by lottery in blocks of 20 so 50 of the infants were studied while flat prone first and 50 were studied while head-elevated prone first Outcome measures: minutes with pH <4, number of episodes with pH <4, mean duration of such	**to less than 4 and ending when the pH rose to greater than 4** 1. Minutes with pH <4/120 mins, mean ± SEM: flat prone- 34.6 ± 3.3, head elevated- 27.8 ± 3.2, p:not significant 2. Number of episodes with pH <4, mean ± SEM: flat prone- 7.8 ± 0.8, head elevated- 6.2 ± 0.6, p: not significant 3. Mean duration of such episodes, mean ± SEM: flat prone- 6.2 ± 0.9, head elevated- 6.1 ± 1.0, p: not significant 4. Number of such episodes lasting longer than 5 minutes, mean ± SD: flat prone- 1.5 ± 0.2, head-elevated: 1.3 ±0.2, p: not significant 5. Duration of the longest episode, mean ± SEM: flat prone- 17.9 ± 2.2, head elevated- 17.1 ± 2.4, p: not significant Resolution of faltering growth Not reported Adverse outcomes	comparable at baseline - yes, crossover trial therefore infants act as their own control for each comparison Level of bias: low B Performance bias B1 - Did groups get same level of care - yes B2 - Were participants blinded to treatment allocation- NA B3 - Were individuals administering care blinded to treatment allocation- NA Level of bias: low C Attrition bias C1 - Was follow-up equal for both groups - yes C2 - Were groups comparable for dropout - yes, no dropout C3 - Were groups comparable for missing data - yes Level of bias: low D Detection bias D1 - Was follow-up appropriate length - yes D2 - Were outcomes defined precisely - yes D3 - Was a valid and reliable method used to assess outcome - yes D4 - Were investigators blinded to intervention - yes, pH probes analysed blindly D5 - Were investigators blinded to confounding

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	probe consisted of esophageal pH <4 for more than 10% of the total time **Histologic documentation of abnormal reflux was defined as papillary height more than 65% of the epithelial height, basal cell thickness more than 20% of the epithelial height, or eosinophilic or polymorphonuclear leukocytes infiltrating the epithelium **Exclusion criteria** - Lack of a clinical research center bed or investigator time to enrol them (n=48) - Lack of parental consent (n=7) - Technical difficulties (n=2)		episodes, number of such episodes lasting longer than 5 minutes, duration of the longest episode. Statistical methods: Data for the 2 positions were compared by paired student t test for data subject to parametric methods and by McNemar test for data requiring nonparametric methods. Significance was defined as p<0.05.	Not reported Parent reported reduction in infant distress Not reported Improvement in validated reflux questionnaire Not reported Parent satisfaction with this intervention Not reported	factors - unclear Level of bias: low Indirectness Does the study match the review protocol in terms of Population: yes Intervention: yes Outcomes: yes Indirectness: none **Other information** Type of position - Though not explicitly stated, it seems as though sleeping/resting position was examined - Infant was positioned after feed (postprandial study period)
Full citation Orenstein,S.R., Whitington,P.F., Orenstein,D.M., The infant seat as treatment for gastroesophageal reflux, New England Journal of Medicine, 309, 760-763, 1983 **Ref Id**	**Sample size** N=9 **Characteristics** Age Range: 0.5 to 4.2 months Mean: 2.2 months Gender Not reported	**Interventions** Infant seat elevated at 60 degrees versus horizontal prone position	**Details** Consent: parental consent obtained Setting: children's medical center Sample size calculation: not reported Method: - After preliminary evaluation, each infant was studied with the esophageal pH probe during a pair of 2 hour postprandial periods, the	**Results** Reduced frequency of overt regurgitation Not reported Reflux* measured using oesophageal pH metry/impedance monitoring ***Reflux episodes were defined as pH <4 for more than 10% of a postprandial period**	**Limitations** NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials A Selection bias A1 - Was there appropriate randomisation - yes A2 - Was there adequate concealment - unclear A3 - Were groups comparable at baseline - yes,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
238057 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial - crossover **Aim of the study** To undertake a prospective controlled comparison of positioning in an infant seat with the prone position for the treatment of gastroesophageal reflux in children under 6 months of age **Study dates** Not reported **Source of funding** Not reported	<u>Weight</u> Not reported <u>Underlying medical conditions</u> Not reported <u>Presenting symptoms, n/N</u> Vomiting: 7/9 Failure to thrive: 3/9 Spells (apnea, cyanosis, stiffening or mouthing): 4/9 Pulmonary symptoms (cough, pneumonia, bronchitis, abnormal chest film): 4/9 Irritability: 5/9 Anorexia: 1/9 **Inclusion criteria** - Children younger than 6 months who were referred to the gastroenterology service for evaluation for gastroesophageal reflux during a 6 week period and in whom gastroesophageal reflux* had been documented by preliminary overnight pH probe evaluation *Gastroesophageal reflux was defined as pH <4 for more than 10% of a postprandial period during a 12 hour esophageal pH monitoring session		order of which was determined by lottery - During one period, the child was continuously positioned at 60 degrees elevation in an infant seat - The seat's strap was loosely fastened to avoid applying pressure to the infant's abdomen - During the other period, the infant was kept in the horizontal prone position - Equal durations of fasting preceded both trials - Before both trials, each patient was fed from a single lot identical volumes (according to individual appetite) of apple juice with a pH below 4.5. - All infants were thoroughly burped before both trials - Outcomes were pH esophageal monitoring parameters following a 2 hour postprandial feed of apple juice <u>Randomisation method:</u> the order in which the positions were studied in each infant was randomly assigned by lottery <u>Outcome measures:</u> percentage of time during the 2 hour postprandial period spent with pH <4, number of episodes with pH <4, number of such episodes lasting longer than 5 minutes, duration of the longest episode. <u>Statistical methods:</u> Data for the 2 positions were compared by paired student t test	**during a 12 hour esophageal pH monitoring session** 1. Percentage of time with distal esophageal pH <4, mean ± SEM: Infant seat - 28.2 ± 6.4, Prone position - 12.8 ± 3.7; p=0.023 2. Number of episodes with pH <4: Infant seat - 16.0 ± 2.4, Prone position - 10.1 ± 2.3; p=0.002 3. Number of such episodes lasting longer than 5 minutes: Infant seat - 1.7 ± 0.6, Prone position - 0.6 ± 0.3; p=0.093 4. Duration of the longest episode, mean ± SEM: Infant seat - 6.7 ± 1.3, Prone position - 4.0 ± 0.8; p=0.079 <u>Resolution of faltering growth</u> Not reported <u>Adverse outcomes</u> Not reported <u>Parent reported reduction in infant distress</u> Not reported <u>Improvement in validated reflux questionnaire</u>	crossover trial therefore infants act as their own control for each comparison Level of bias: low B Performance bias B1 - Did groups get same level of care - yes B2 - Were participants blinded to treatment allocation- NA B3 - Were individuals administering care blinded to treatment allocation- NA Level of bias: low C Attrition bias C1 - Was follow-up equal for both groups - yes C2 - Were groups comparable for dropout - yes C3 - Were groups comparable for missing data - yes Level of bias: low D Detection bias D1 - Was follow-up appropriate length - yes D2 - Were outcomes defined precisely - yes D3 - Was a valid and reliable method used to assess outcome - yes D4 - Were investigators blinded to intervention - unclear D5 - Were investigators blinded to confounding factors - unclear Level of bias: low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria Not reported			Not reported Parent satisfaction with this intervention Not reported	Indirectness Does the study match the review protocol in terms of Population: yes Intervention: yes Outcomes: yes Indirectness: none **Other information** Type of position - Though not explicitly stated, it seems as though sleeping/resting position was examined - Infant was positioned after feed (postprandial study period)
Full citation Bagucka,B., Acid gastroesophageal reflux in the 10 degrees reversed-Trendelenburg position in supine sleeping infants, Acta Paediatrica Taiwanica, 40, 298-301, 1999 **Ref Id** 262163 **Country/ies where the study was carried out** Belgium	**Sample size** N= 10 **Characteristics** Age 2 to 8 weeks old Gender Not reported Weight Not reported Underlying medical conditions Not explicitly reported but all infants were those currently not on medication	**Interventions** Sleeping position: supine reversed-Trendelenburg position of 10 degrees versus flat supine positioning. (The reversed-Trendelenburg corresponds to the effect obtained by putting two telephone books under the head-side of the bed).	**Details** Consent: not reported Setting: pediatric gastroenterology clinic Sample size calculation: not reported Method: - A one channel 48 hour esophageal pH monitoring was performed - A detailed diary was recorded during the first day and was meticulously repeated on day 2 - In order to avoid hazardous influences such as adaptation of the infant to the presence of the electrode, the first 24 hour recording	**Results** Reduced frequency of overt regurgitation Not reported Reflux* measured using oesophageal pH metry/impedance monitoring *1. Percent of time with distal esophageal pH <4 (reflux index), mean ± SEM (SD): Flat supine - 10.62 ± 2.02 (6.40), Supine reversed Trendelenburg - 19.08 ± 4.14 (13.10); p=0.08* *2. Number of episodes with pH <4, mean ± SEM (SD): Flat supine -*	**Limitations** NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials A Selection bias A1 - Was there appropriate randomisation - unclear, method of randomisation not reported A2 - Was there adequate concealment - unclear A3 - Were groups comparable at baseline - yes, crossover trial therefore infants act as their own control for each comparison Level of bias: unclear B Performance bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Randomised controlled trial - crossover **Aim of the study** Not explicitly stated - to compare acid reflux parameters in the supine reversed Trendelenburg position at 10 degrees in comparison to the flat supine sleeping position **Study dates** Not reported **Source of funding** Not reported	Clinical symptoms Excessive regurgitation **Inclusion criteria** - Parents of infants (aged 2 to 8 weeks old) presenting at an outdoor clinic for Pediatric Gastroenterology because of excessive regurgitation - Exclusively bottle-fed and without any medication **Exclusion criteria** - Not reported		was performed in 5 infants in flat supine and the next day in supine reversed Trendelenburg position and in 5 infants the order of investigation was reversed - The statistical analysis included a Wilcoxon test - Significance was set a p<0.05 Randomisation method: not reported Outcome measures: percent of time with distal esophageal pH <4 (reflux index), number of episodes with pH <4, duration of the longest episode Statistical methods: Wilcoxon test, significance defined as p<0.05	*33.9 ± 4.93 (15.6), Supine reversed Trendelenburg - 32.30 ± 2.53 (8.00); p=0.95* *3. Duration of the longest episode, mean ± SEM (SD): Flat supine - 17.00 ± 2.01 (6.34), Supine reversed Trendelenburg - 38.9 ± 14.8 (46.81); p=0.16* Resolution of faltering growth Not reported Adverse outcomes Not reported Parent reported reduction in infant distress Not reported Improvement in validated reflux questionnaire Not reported Parent satisfaction with this intervention Not reported	B1 - Did groups get same level of care - yes B2 - Were participants blinded to treatment allocation- NA B3 - Were individuals administering care blinded to treatment allocation- NA Level of bias: low C Attrition bias C1 - Was follow-up equal for both groups - yes C2 - Were groups comparable for dropout - yes C3 - Were groups comparable for missing data - yes Level of bias: low D Detection bias D1 - Was follow-up appropriate length - yes D2 - Were outcomes defined precisely - yes D3 - Was a valid and reliable method used to assess outcome - yes D4 - Were investigators blinded to intervention - unclear D5 - Were investigators blinded to confounding factors - unclear Level of bias: low Indirectness Does the study match the review protocol in terms of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Population: yes Intervention: yes Outcomes: yes Indirectness: none **Other information** Study does not specifically state that this was a randomised controlled trial. <u>Type of position (sleeping/resting/feeding)</u> Sleeping position was examined (unclear if position was altered during feeds)

I.6 What is the effectiveness of a managed feeding regimen in comparison with a conventional, age appropriate, regimen in the management of overt GOR?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Miyazawa,R., Tomomasa,T., Kaneko,H., Arakawa,H., Morikawa,A., Effect of formula thickened with reduced concentration of locust bean gum on gastroesophageal reflux, Acta Paediatrica, 96, 910-914, 2007 **Ref Id** 219363 **Country/ies where the study was carried out** Japan **Study type** Randomised controlled trial; cross-over **Aim of the study** To determine clinical applicability of HL-350 in terms of sucking time and gastric emptying delay in younger infants with GER. **Study dates** January 2001 to August	**Sample size** 20 No dropouts **Characteristics** As a crossover study only one group: • 8 males, 12 females • 36 days (+/- 13) • 4357.2 g (+/- 584.5g) **Inclusion criteria** Aged < 2 months 3 or more episodes of regurgitation per day, but not symptoms suggesting GER-related complications **Exclusion criteria** • Neurological disabilities • Known organic or metabolic causes of GER Major medical problems including low birthweight (<1500g), prematurity (<35 weeks), jaundice, any other gastrointestinal symptoms such as diarrhoea, constipation or	**Interventions** • Locust bean gum (0.35g/100ml) added to standard milk formula (HL-350) • Standard milk formula (HL-00) • 1 week with each formula	**Details** <u>Ethics</u> Ethics approval and informed consent gained <u>Setting</u> University hospital <u>Outcome measurements</u> • Episodes of regurgitation • Weight gain • Feeding volume (ml/day) • Feeding time (minutes) • Bowel movements (day) <u>Protocol</u> Randomly assigned to use HL-00 or HL-350 for first week and then switch to the other the week after. <u>Statistical analyses</u> Wilcoxon's signed rank test No further information provided	**Results** **Outcome: HL-00, HL-350, median (range)** Episodes of regurgitation per day: 5.2 (3.7 to 7.8), 2.3 (1.6 to 3.6) Weight gain (g/day): 20.8 (13.2 to 29.6), 30.6 (20.4 to 37.4)	**Limitations** Method of randomisation and concealment not described in detail 5 infants received supplemental breast feeds. **Other information** One of three papers published by authors on use of locust bean gum. Authors do not say that studies are linked, but carried out over same period and have same date of ethics approval.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
2006. **Source of funding** Not stated	abdominal distension, or previous drug treatment for GER.				
Full citation Miyazawa,R., Tomomasa,T., Kaneko,H., Arakawa,H., Shimizu,N., Morikawa,A., Effects of pectin liquid on gastroesophageal reflux disease in children with cerebral palsy, BMC Gastroenterology, Vol.8, pp.11, 2008., -, -32676 **Ref Id** 219383 **Country/ies where the study was carried out** Japan **Study type** Randomised controlled trial **Aim of the study** Investigated the effects of thickening of food with two different concentrations of pectin liquid on acid exposure	**Sample size** 18 **Characteristics** • 18 female and 2 male • Mean average age 11.7 years (+/- 4.4) • 10 of 18 had previously been treated with H2Rs **Inclusion criteria** • Cerebral palsy • Receiving feed through naso-gastric tube. • Clinical suspicion of GERD based on symptoms (recurrent vomiting, chronic cough, recurrent pneumonnia) or pH study (RI = pH < 4.0 for 4% of time). **Exclusion criteria**	**Interventions** • High concentration pectin (2:1 ratio enteral formula :pectin liquid) • Low concentration pectin (3:1 ratio enteral formula :pectin liquid) • Non-pectin formula Each feed regimen given for 4 week period	**Details** **Ethics** Not stated **Setting** University hospital **Method of randomisation and blinding** Randomised to Group A or Group B Group A received High concentration pectin and non-pectin diet Group b received low pectin diet and non-pectin diet. Unclear if infants were randomised to which feed regimen was received or if assigned. Different nurse prepared feed to those who recorded outcomes **Outcome measurements** • Number of reflux episodes • Number of reflux episodes > 5 minutes • Duration of longest reflux episode (minutes) • Number of vomits per week • Gastric bleeds per week • Gastric reside (>25ml per week • Total gastric reside	**Results** Group A (high pectin): pectin -, pectin + Number of reflux episodes per day: 151 (94 to 205)(p<0.05), 100 (72 to 113) Group B (low pectin) pectin -, pectin + Number of reflux episodes per day: 112, (62 to 139), 146 (72 to 153) Number of vomiting episodes per week: 2.5 (1 to 5)(P<0.05), 1 (1 to 1.5) Group B (low pectin) pectin -, pectin + Number of vomiting episodes per week: 0, (0 to 0.5), 0 (0 to 0)	**Limitations** Method of randomisation not explained in detail **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and symptoms that might be attributed to GER in children with cerebral palsy **Study dates** Not stated **Source of funding** Not stated	• Surgical treatment for GERD		• Cough & wheeze • Desaturation/week **Statistical analyses** X^2, unpaired t-test or Wilcoxon's signed rank test **Monitoring using:** • pH monitoring for 48 hours Nurse data recording of feeds and clinical symptoms.		
Full citation Vanderhoof,J.A., Moran,J.R., Harris,C.L., Merkel,K.L., Orenstein,S.R., Efficacy of a pre-thickened infant formula: a multicenter, double-blind, randomized, placebo-controlled parallel group trial in 104 infants with symptomatic gastroesophageal reflux, Clinical Pediatrics, 42, 483-495, 2003 **Ref Id** 219390 **Country/ies where the study was carried out** USA	**Sample size** 110 recruited and randomised. 6 did not start study 104 infants included in analysis AR = 55, Control = 49 (1 excluded due to protocol voilation = 48) Completed study: 84% (9); 73% (12) **Characteristics** • Characteristics: Enfamil AR (n = 55), Control (n = 49) • Gender (M:F): 27/28, 26.23 • Age (days): 61 (4), 58 (4) • Formula used - 85% cow's milk, 13% soy, 2% hydrolised; 86% cow's milk, 12% Soy,	**Interventions** • Control: standard commercially available cow-milk formula (not specified) for 5 weeks • Enfamil AR (rice starch) for 5 weeks - Volume and frequency of feeding at the parents decision - Standard feeding nipple used	**Details** <u>Ethics</u> Ethics approval and informed consent <u>Setting</u> Six paediatric clinics <u>Study protocol</u> • Randomised at study site • Blinded allocation <u>Outcome measurements</u> • Frequency of regurgitation based on diary • Volume of regurgitation based on diary • Volume of formula consumed based on diary <u>Statistical analyses</u> Cochran-Mantel-Haenszel test stratified by site	**Results** <u>Outcome: Enfamil AR; Control</u> • Regurgitation frequency per day: 6 (+/- 1), 6 (+/-1), NS • Regurgitation frequency (change % of feeds): -38% (+/-5), -24 (+/-5), NS • Used pharmacotherapy: 4%, 2%, NS • Discontinued due to formula: 13%; 20%, NS • Serious adverse events: 1; 2, NS	**Limitations** • Unclear what presented figures represent means or medians - Method of randomisation and concealment not described in detail - High discontinuation rate in control group (27%) - Additional treatment received by children nopt specified **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Randomised controlled trial **Aim of the study** Evaluate the efficacy of Enfamil AR in young infants with regurgitation GER. **Study dates** December 1996 to July 1998 **Source of funding** Mead Johnson & Co	2% hydrolised **Inclusion criteria** • >=5 regurgitations per day during baseline period • Aged 14 to 120 days • Gestational age at birth >37 weeks • Birth weight >=2500g • Maternal age > 18 years. • Formula fed **Exclusion criteria** • Disease or congenital anomalies interfering with normal feeding • Fever or infectious illness at enrolment • Diagnosed with milk or soy protein allergy Complicated GORD (oesophagitis, hematemesis, recurrent respiratory symptoms, failure to thrive, etc.), previous treatment with thickened formula or prokinetic medication.				
Full citation Ostrom,K.M.,	**Sample size**	**Interventions** - Group 1: Soy-based	**Details** Setting	**Results** Number of daily	**Limitations** 44 infants did not

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Jacobs,J.R., Merritt,R.J., Murray,R.D., Decreased regurgitation with a soy formula containing added soy fiber, Clinical Pediatrics, 45, 29-36, 2006 **Ref Id** 237184 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** Compare fiber-supplemented soy formula reduced regurgitation compared cow's milk-based formula. **Study dates** Not stated **Source of funding** Abbott Laboratories	• 199 infants were enrolled. • 179 were randomised • 23 discontinued from cow's milk arm (mainly intolerance) • 21 discontinued from soy formula arm (mainly intolerance). • 135 completed the study **Characteristics** • Aged 13 to 32 days. Mean age 19 days in both groups. • 84% were cow's milk formula fed, 9% soy formula and 7% were unknown. • Frequency of feeding was 7 to 8 times per day • Weight gain was 32 to 33g/day in both groups. **Inclusion criteria** • Parents report that regurgitation associated with 25% or more of feeds • Singleton birth	formula plus 6g of added soy fiber per litre (Isomil). - Group 2: Milk-based formula alone (Similac) - Positioning during and after feeds was left to parents. Parents agreed not to use any other supplements or medicines.	Recruited in well-baby clinics from six sites; infants fed at home. <u>Randomisation</u> • Computer generated blocks by site. • Double blinded – parents and study personnel <u>Outcomes</u> Primary outcome: • Daily incidence of regurgitation (mean average during study period based on parent reports). Secondary: • Mean average number of feeds associated with regurgitation. • Percentage of infants with reflux not associated with feeding • Percentage of subjects with any regurgitation • Volume of intake • Mean size of regurgitation • Parent response to questionnaire on regurgitation and tolerance • Infant weight.	regurgitations: Soy feed, Milk feed, mean (SEM): • Baseline = 3.9 (0.2), 3.6 (0.2) • Day 7 = 2.3 (0.2), 3.4 (0.2) • Day 28 = 2.0 (0.2), 2.4 (0.3), p = 0.029 Percentage of feeds associated with regurgitation: Soy feed, Milk feed, mean (SEM): • Baseline = 50.9 (3.1), 48.6 (3.0) • Day 7 = 31.0 (2.4), 48.3 (4.2) • Day 28 = 28.8 (3.8), 36.0 (4.2) p = 0.015 Number of infants with any regurgitation: Soy feed, Milk feed, mean (SEM): • Baseline = 87/87, 90/90 • Day 7 = 86/87, 85/85 • Day 28 = 56/67, 63/66, p = 0.027	complete study (25%). Combines thickening feed and removing Cow's milk, so unclear which is having an effect. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• 37 to 42 weeks gestation • Birth weight > 2500 g **Exclusion criteria** • Maternal, fetal or perinatal history thought to be negative effect on tolerance, growth or development. • History of pyloric stenosis or other associated vomiting		• Adverse events <u>Statistical analyses</u> • Intention to treat analysis undertaken • Covariance of site and level of baseline regurgitation (< or > 30% of feeds).	>30% regurgitation at baseline • Day 28 = <50%, <35%, <30% regurgitation at baseline • Day 28 = <68%, <39% No relationship between severity of regurgitation and feeding group (p = 0.651)	
Full citation Xinias,I., Mouane,N., Le,Luyer B., Spiroglou,K., Demertzidou,V., Hauser,B., Vandenplas,Y., Cornstarch thickened formula reduces oesophageal acid exposure time in infants, Digestive and Liver Disease, 37, 23-27, 2005 **Ref Id** 219276 **Country/ies where the**	**Sample size** 96 children randomised (45 regular formula, 51 thickened formula). **Characteristics** Variable: regular formula, thickened formula • Age (days): 94 (32), 92 (35) • Weight baseline (g): 4803 (707), 4905 (836) • Regurgitation/day: • 4.77 (2.35), 5.60 (4.15) • Vomiting/day: 3.09	**Interventions** - Regular formula (not specified) - Re-gelatinised corn-starch used to thicken regular formula	**Details** <u>Setting:</u> • Not specified, but in 4 units in four countries. • Ethics approval obtained • Randomised (sealed envelopes) • Double blind <u>Protocol</u> • pH monitoring of acid reflux at baseline and after 26 day (+/- 5 days) • Parent record of regurgitation, vomiting and	**Results** Outcome: regular formula, thickened formula at end of study Episodes of regurgitation/day 4.31 (2.01), 2.57 (2.71) Episodes of vomiting/day 2.74 (1.37), 1.45 (1.65) Weight gain per day 24.3 (8.1), 28.5 (12.1) Reflux index 11.4 (7.0), 6.8 (6.2) Number of reflux episodes per hour 8.7 (4.9), 6.2 (10.2) Number of reflux episodes > 5 minutes 5.4 (4.2), 2.9 (3.4) Longest reflux episodes (minutes)	**Limitations** • Method of randomisation and allocation concealment not described in detail • Structure of allocation to different sites not explained **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study was carried out Greece, France, Morocco, Belgium **Study type** Randomised controlled trial **Aim of the study** Efficacy of an infant formula thickened with a specifically treated cornstarch versus standard infant formula to reduce oesohageal acid exposure time in exclusively formula fed infants with regurgitation. **Study dates** Not stated **Source of funding** United pharmaceuticals provided products	(1.24), 4.34 (2.42) No difference in pH characteristics at baseline **Inclusion criteria** • Formula-fed • Presenting with troublesome regurgitation and/or vomiting • Not previously treated for reflux • 'Healthy' except for excessive regurgitation **Exclusion criteria** • Very irritable • Had hematemesis • Black stools • Chronic cough • Episodes of cyanosis Any other medical problem		defecation <u>Outcome measures</u> <u>pH outcomes</u> - Reflux index - Number of reflux episodes per hour - Number of relfux episodes > 5 minutes - Duration of longest reflux episode <u>Parent reported outcomes</u> - Number of regurgitation episodes per day - Number of vomiting episodes per day - Weight gain per day (g) <u>Statistical analyses</u> Unpaired t-test or Wilcoxon rank test	19.3 (10.5), 10.8 (8.9)	
Full citation Chao,H.C., Vandenplas,Y., Comparison of the effect of a cornstarch thickened formula and strengthened regular	**Sample size** • 100 entered study • 81 completed study • Group cornstarch = 41,	**Interventions** - Cornstarch-thickened AR-formula (Novalac AR) for 8 weeks - 25% strengthened regular formula (Novalac) 5 measurements instead	**Details** <u>Ethics</u> Not mentioned <u>Setting</u> Pediatricians 'outdoor' clinic <u>Method of randomisation</u>	**Results** **1-month** **Outcome: Cornstarch, Regular; mean (SD)** • Frequency of regurgitation/vomit	**Limitations** - Randomisation and concealment not described in detail - Comparison group had partially strengthened formula. - 20% discontinuation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
formula on regurgitation, gastric emptying and weight gain in infantile regurgitation, Diseases of the Esophagus, 20, 155-160, 2007 **Ref Id** 219256 **Country/ies where the study was carried out** Taiwan **Study type** Randomised controlled trial **Aim of the study** Effect of a cornstarch-thickened formula or 25% strengthened formula in the treatment of regurgitation and vomiting in infants. **Study dates** July 2002 to July 2004 **Source of funding** Not stated	Regular = 40 **Characteristics** Characteristic: group A, group B • Age (days): 90.2 (26.9), 90.5 (27.4) • Sex (M/F): 21/20, 21/19 • Body weight (g): 5423.4 (845.7), 5466.1 (857.3) **Inclusion criteria** • Non-breast fed • Aged 2 to 4 months • 3 or more episodes of regurgitation/vomiting per day **Exclusion criteria** - Mechanical obstruction such as infantile hypertrophic pyloric stenosis or malrotation. - Infant's with atopic symptoms such as eczema, watery rhinorrhea or diarrhoea suspecting Cow's milk allergy	of 4 added to 120 ml water for 8 weeks	Randomisation using envelope-drawing system <u>Outcome measurements</u> • Gastric emptying using scintigraphy • Regurgitation/vomiting as reported by parents • Reflux symptoms **For**mulas used for 8 weeks <u>Statistical analyses</u> Paired Student t-test, Wilcoxon signed rank test, and Chi-square	ing: 1.90 (0.72), 3.15 (0.93) • Irritability: 4, 10 • Crying awake: 1, 4 **8-weeks** • Frequency of regurgitation/vomiting: 0.93 (0.42), 2.89 (1.16) • Irritability: 1, 8 • Crying awake: 1, 2	from study **Other information**
Full citation	**Sample size** 20 infants	**Interventions**	**Details** <u>Setting</u>	**Results** Variable: group 1, group 2	**Limitations** Method randomisation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Vandenplas,Y., Hachimi-Idrissi,S., Casteels,A., Mahler,T., Loeb,H., A clinical trial with an "anti-regurgitation" formula, European Journal of Pediatrics, 153, 419-423, 1994 **Ref Id** 246414 **Country/ies where the study was carried out** Belgium **Study type** Randomised controlled trial **Aim of the study** Evaluate the efficacy of a anti-regurgitation formula on the incidence of regurgitation in babies. **Study dates** Not stated **Source of funding** Not stated	**Characteristics** Not stated **Inclusion criteria** • 1 to 4 months of age • Presenting with frequent regurgitation (more than 5 times per day) • pH monitoring results <4.0 for between 10% and 30% of time. • Full-term • Formula fed **Exclusion criteria** • Reflux secondary to urinary or gastrointestinal infection or food allergy were excluded after testing	• Group 1: standard formula, positional treatment and reassurance for 1 week • Group 2: antiregurgitation formula, positional treatment and reassurance for 1 week • Same formula except for thickener. 3 days of formula and 1 day of pH monitoring.	Out-patient clinic <u>Protocol</u> Infants randomised to one of two group Double blind <u>Monitoring</u> 24-hour pH monitoring Regurgitation reported by parent diary <u>Outcome measurements</u> • Reflux index • Duration of longest reflux • Number of reflux epsidoes > 5 minutes • Regurgitation severity score <u>Statistical analyses</u> Unpaired t-test	Reflux index 13.2 (4.7), 11.1 (6.1) Duration of longest episode: 29.9 (18.9), 31.1 (23.4) Number > 5 minutes: 8.80 (2.90), 7.70 (4.27)	and concealment not described in detail

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Sutphen,J.L., Dillard,V.L., Effect of feeding volume on early postcibal gastroesophageal reflux in infants, Journal of Pediatric Gastroenterology and Nutrition, 7, 185-188, 1988 **Ref Id** 237764 **Country/ies where the study was carried out** USA **Study type** Comparative clinical trial **Aim of the study** Document the effects of feeding volume on early postcibal GER oberveed in infants during pH probe. **Study dates** Not stated	**Sample size** 50 (8 preterm) **Characteristics** • Mean age 4 months (2 months preterm to 32 months) • Mean weight 5.3kg (1.3 to 10.83kg). **Inclusion criteria** • GER symptoms (vomiting, apnoea, choking or pulmonary symptoms) • GER then measured using pH monitoring - definition of GER not specified **Exclusion criteria** • Structural cause of GORD or post surgical GORD	**Interventions** First 25 infants given two feedings of clear liquid (5% dextrose water), one feeding of 9 ml/kg and one of 18 ml/kg Next 16 infants received feed of 9 ml/kg and an ad libitum volume (mean 27.3 (SD 9.8). 9 infants did not receive correct feeding volumes.	**Details** <u>Setting</u> Referred to hospital for evaluation of GER <u>Study protocol</u> All children had 24 hour pH monitoring <u>Outcomes</u> • Number of GER episodes • Duration of longest GER episode <u>Statistical analyses</u> • Multiple regression model • Paired t-tests	**Results** 6 infants did not demonstrate GER symptoms during observation and formed control group Total GER episodes within 1 hour: 9 ml/kg = 8.1 (SD 13.9), 18 ml/kg = 14.3 (SD12.5), p = 0.004 Longest episode: 9 ml/kg = 5.0 (SD 11.9), 18 ml/kg = 7.3 (SD5.8), p = 0.009	**Limitations** Observational study design Intervention varied within study. Study protocol appears to have varied.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not stated					
Full citation Moukarzel,A.A., Abdelnour,H., Akatcherian,C., Effects of a prethickened formula on esophageal pH and gastric emptying of infants with GER, Journal of Clinical Gastroenterology, 41, 823-829, 2007 **Ref Id** 219373 **Country/ies where the study was carried out** USA **Study type** Open lable, randomised controlled trial **Aim of the study** Compare the effects on oesophageal pH and gastric emptying of prethickened formula with regular formula. **Study dates** Not stated	**Sample size** 74 infants 60 Analysed (32 regular, 28 prethickened) **Characteristics** Not described **Inclusion criteria** • Aged <= 6months • Diagnosed with GER based on I-GERQ (cut-off not specified) **Exclusion criteria** • Breast fed • Premature • History of wheezing, aspiration pneumonia, apnoea, failure to thrive, anaemia, bleeding, laryngitis and ALTE.	**Interventions** - Prethickened formula (Not specified), but viscosity was 10x that of regular formula. - Regular formula (not specified) - Both produced by Wyeth Nutritional. - Treatment for 1 month.	**Details** <u>Ethics</u> Ethics approval granted <u>Setting</u> Not specified <u>Protocol</u> Two-stage study. Stage 1 - All infants underwent 24-hour pH-monitoring with alternating treatment between prethickened and regular formula for 3 or 4 feeds Stage 2 - Infants randomised to either thickened or regular formula for 1 month <u>Outcome measurements</u> Longest reflux episode Number of reflux episodes > 5 minutes Reflux Index Incidence of regurgitation (not pH-monitoring) Indidence of vomiting (not pH-monitoring) <u>Monitoring</u> pH monitoring Severe GORD defined as RI of >10% Electrogastrography to monitor	**Results** 6 from regular and 8 from prethickened were excluded from study due to GERD symptoms requiring treatment. Outcome: regular, mean (SD) (n = 32); prethickened , mean (SD)(n = 28); prethickened-Regular mean difference (SD); p-value • Number of reflux episodes > 5 minutes: 1.37 (1.68), 1.61 (2.68), 0.24 (0.67), p = 0.43 • Longest reflux episode (min):11.35 (10.86), 5.86 (5.22), -5.50 (5.25), p <0.0001 • RI (%): 7.77 (7.72), 5.64 (5.14), -2.13 (6.80), p < 0.0087 Incidence of regurgitation: mean (SD) Baseline: 6.5 (3.7), 7.1 (3.9) 4 weeks: 5.2 (3.1), 2.3 (2.0)	**Limitations** • Method of randomisation not described in detail. • Open label study so no allocation concealment and blinding of treatment. • 19% excluded from analysis due to reflux symptoms

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Wyeth Nutritionals and St John University research fund			gastric emptying. <u>Statistical analyses</u> Intention to treat Paired t-test or Fisher exact test.	Incidence of vomiting: Regular vs Thickened;mean (SD) Baseline: 2.1 (3.0), 2.6 (2.6) 4 weeks: 1.2 (1.1), 0.5 (0.8) Incidence of regurgitation: Regular vs Thickened; mean (SD) Baseline: 6.5 (3.7), 7.1 (3.9 4 weeks: 52 (3.1), 2.3 (2.0) Outcome of pH monitoring: pretickened-regular severe GER, mean difference (SD) (n = 23); prethickened-regular mild to moderate GER , mean difference (SD)(n = 51); ; p-value • Number of reflux episodes > 5 minutes: -2.52(0.91), 1.49(2.21), p < 0.0001 • Longest reflux episode (min): -19.13 (7.72), -0.65 (2.64), , p <0.0001 • RI (%): -8.77 (8.06), -0.86 (3.07), p < 0.002	
Full citation Miyazawa,R.,	**Sample size** 39 infants	**Interventions** • Locust bean	**Details** <u>Details</u> Ethics approval obtained	**Results** <u>Regurgitation episodes during study period</u>	**Limitations** Method of randomisation and concealment not

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Tomomasa,T., Kaneko,H., Morikawa,A., Effect of formula thickened with locust bean gum on gastric emptying in infants, Journal of Paediatrics and Child Health, 42, 808-812, 2006 **Ref Id** 237723 **Country/ies where the study was carried out** Japan **Study type** Randomised controlled trial; crossover within arms **Aim of the study** Examine milk-based formula thickened with two different concentrations of locust bean gum on gastric emptying in infants with recurrent regurgitation episodes. **Study dates** Not stated	**Characteristics** Not defined for groups in 2nd part of the study **Inclusion criteria** 3 or more episodes of regurgitation per day, but not symptoms suggesting GER-related complications **Exclusion criteria** - Neurological disabilities - Known organic or metabolic causes of GER - Major medical problems including low birthweight (<2000g), prematurity (<35 weeks), jaundice, any other gastrointestinal symptoms such as diarrhoea, constipation or abdominal distension, or previous drug treatment for GER.	gum (0.35g/100ml) added to standard milk formula (HL-350) • Locust bean gum (0.45g/100ml) added to standard milk (HL-450) formula • Standard milk formula (HL-00) Treatments used for 1 week.	Setting University hospital Outcome measurements Regurgitation episodes as reported by parent (Other outcomes reported in graphical format) Methods Randomised to 2 groups. • Group A HL-00 and HL-350. • Group B HL-00 and HL-450. Infants randomised to which formula they used first within each group. Each formula used for one week before being switched. No washout period between formulas. Statistical analyses X^2, Kruskal-Wallis test, Mann-Whitney u-test or Wilcoxon's signed rank test.	Group A (n = 13), mean (SD) HL-00, HL-350 22.6 (3.9), 12.9 (3.5) Group B (n = 14), mean (SD) HL-00, HL-450 29.8 (3.6), 12.8 (3.0)	described in detail. Unclear to which part of treatment protocol randomisation applied. No washout period between feeds reported **Other information** Two stage study. First stage (not reported) examined gastric emptying. Infants randomly assigned to one of 3 treatment groups. Second stage reported outcomes of interest. One of three papers published by authors on use of locust bean gum. Authors do not say that studies are linked, but carried out over same period and have same date of ethics approval.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Government grant from The Ministry of Education, Science, Sports and Culture in Japan					
Full citation Orenstein,S.R., Magill,H.L., Brooks,P., Thickening of infant feedings for therapy of gastroesophageal reflux, Journal of Pediatrics, 110, 181-186, 1987 **Ref Id** 237755 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial; cross-over **Aim of the study** Evaluate the effect of the thickening of infant formula on scintigraphically measured GER, on actual regurgitation with loss of formula, on gastric emptying, and	**Sample size** • 21 infants • 20 completed the study **Characteristics** Aged 4 to 34 weeks No other information provided **Inclusion criteria** Aged 1 year or younger Diagnosis of GER based on symptoms and/or abnormal test results from pH monitoring or endoscopy. **Exclusion criteria** None stated	**Interventions** Infants regular formula with or without dry rice cereal (15ml/30ml) for a single feed	**Details** <u>Ethics</u> Ethics approval gained <u>Setting</u> Medical centre <u>Protocol</u> Random allocation to which feed was used first. <u>Outcome measurements</u> - Frequency of emesis in 90 minutes Crying time Sleep time Gatsric emptying Gastric reflux by scintigraph <u>Statistical analyses</u> Wilcoxon signed rank test <u>Monitoring</u> scintigraphically wasout period of 48 to 72 hours Infant examined in 90 minutes after feed Those assessing outcomes were blinded to allocation Randomisation in block of 20	**Results** Emesis Episodes in 90 minutes, mean (SD): unthickened, thickened 3.9 (0.9), 1.2 (0.7)	**Limitations** Single feed for each arm. Method of monitoring was invasive Method of randomisation and concealment not described in detail **Other information** Use of cross-over design and method of reporting means figures cannot be used in meta-analysis

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
on behaviour. **Study dates** Not stated **Source of funding** Grant from American College of Gastroenterology					
Full citation Miyazawa,R., Tomomasa,T., Kaneko,H., Morikawa,A., Effect of locust bean gum in anti-regurgitant milk on the regurgitation in uncomplicated gastroesophageal reflux, Journal of Pediatric Gastroenterology and Nutrition, 38, 479-483, 2004 **Ref Id** 237850 **Country/ies where the study was carried out** Japan **Study type** Randomised controlled trial; crossover	**Sample size** 30 infants **Characteristics** Characteristic: Group A, Group B • Sex (% female): 56.3, 36.4 • Age (days): 130.9 (20.8), 124.5 (17.7) • Body weight (g): 6726.3 (720.5), 6815.0 (636.4) • Supplemental breast feeding: 2, 5 **Inclusion criteria** Not defined for groups in 2nd part of the study 3 or more episodes of regurgitation per day, but not symptoms suggesting GER-related complications	**Interventions** • Locust bean gum (0.35g/100ml) added to standard milk formula (HL-350) • Locust bean gum (0.45g/100ml) added to standard milk (HL-450) formula • Standard milk formula (HL-00) Treatments used for 1 week.	**Details** **Ethics** Ethics approval and informed consent gained Setting University hospital Outcome measurements Statistical analyses X^2 test and unpaired Student t-test. Protocol Randomised to 2 groups. • Group A HL-00 and HL-350. • Group B HL-00 and HL-450. Infants randomised to which formula they used first within each group. Each formula used for one week before being switched. No washout	**Results** **Frequency of regurgitation, median (IQR)** HL-450 1.6 (IQR 0.8 to 2.0), HL-00 3.5 (IQR 2.3 to 4.9) HL-450 1.3 (IQR 0.6 to 2.3), HL-00 2.9 (IQR 2.0 to 3.2) No complications reported during study period	**Limitations** Method of randomisation and concealment not described in detail. Unclear to which part of treatment protocol randomisation applied. No washout period between feeds reported **Other information** Study did not appear to compare groups across the cross-over, but only within the arm. Ethics approval gained after study had finished

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study Study on the number and volume of regurgitation, the feeding time and the volume consumed, weight gain and bowel movement frequency in infants fed formula thickened with different concentrations of locust bean gum. **Study dates** August 2000 to August 2001 **Source of funding** Government grant from The Ministry of Education, Science, Sports and Culture in Japan	**Exclusion criteria** • Neurological disabilities • Known organic or metabolic causes of GER Major medical problems including low birthweight (<2000g), prematurity (<35 weeks), jaundice, any other gastrointestinal symptoms such as diarrhoea, constipation or abdominal distension, or previous drug treatment for GER.		period between formulas.		
Full citation Nielsen,R.G., Bindslev-Jensen,C., Kruse-Andersen,S., Husby,S., Severe gastroesophageal reflux disease and cow milk hypersensitivity in infants and children: disease association and evaluation of a new challenge procedure,	**Sample size** 51 children invited 45 accepted to join 42 assessed for inclusion 18 children had GERD (oesophagitis or RI > 10%) **Characteristics** Median age: 104 months, range 2 to 178	**Interventions** Two sets of Cow's milk challenge undertaken	**Details** <u>Ethics</u> Ethics approval obtained <u>Setting</u> Admitted to University hospital <u>Classification of GERD</u> Endoscopic findings or Reflux Index > 10% <u>Classification of CMH</u> Skin prick/patch tests for milk, soy	**Results** Outcome: GERD, GERD with Cow's milk hypersensitivity Number: 7, 10 Reflux Index (median): 7.7, 15.6. p = 0.03 Reflux index day1 vs day 2: 8.4 vs 10.0, 14.0 vs 17.5, NS	**Limitations** Complex study design Analysis separates children between those with and without Cow's milk hypersensitivity. Small sample size

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Journal of Pediatric Gastroenterology and Nutrition, 39, 383-391, 2004 **Ref Id** 219988 **Country/ies where the study was carried out** Denmark **Study type** Comparative crossover observational study **Aim of the study** 1) Determine whether an association between GERD and cow milk allergy/hypersensitivity could be identified in infants and older children. 2) If Cow's milk challenge during pH monitoring could be used to identify GERD-CMH subgroup 3) Evaluate the effect of elimination diet on reflux parameters **Study dates** Not stated, but people recruited over a 2 year period	**Inclusion criteria** - Children aged 0 to 15 years - Symptoms of GERD - No previous diagnosis of food hypersensitivity **Exclusion criteria** Known causes of GERD, such as malformations/artresia. Lactase deficiency or H. pylori gastritis were excluded		and peanuts <u>Two stage study</u> <u>Stage 1</u> - Endoscopy under general anesthesia - 48-hour pH monitoring: 24-hours with cow's milk elimination diet, then 24-hours with Cow's milk challenge. Dose depended on age. <u>Stage 2</u> - 4 to 6 weeks on a cow's milk elimination diet followed by a cow's milk challenge. Children aged older than 3 were blinded to allocation, children under 3 had open allocation. <u>Outcomes</u> - Reflux index - Number of reflux epsidoes (pH < 4) - Number of reflux episodes lasting longer than 5 minutes - Post-prandial reflux index		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Grants from the Ronald McDonald House Charities and The Clinical Institute at the University of Southern Denamrk.					
Full citation Borrelli,O., Mancini,V., Thapar,N., Giorgio,V., Elawad,M., Hill,S., Shah,N., Lindley,K.J., Cow's milk challenge increases weakly acidic reflux in children with cow's milk allergy and gastroesophageal reflux disease, Journal of Pediatrics, 161, 476-481, 2012 **Ref Id** 219284 **Country/ies where the study was carried out** UK **Study type** Non-randomised observational crossover trial **Aim of the study** Investigate the effect of Cow's milk challenge on	**Sample size** 24 assessed for inclusion 17 included in study **Characteristics** Median age and range: 11 months (6 to 24 months) **Inclusion criteria** Cow's Milk allergy Suspected GERD (Infant GER Questionnaire revised) Used amino acid based formula for at least 2 months **Exclusion criteria** Not stated	**Interventions** 24-hours on amino acid formula followed by 24-hours milk formula	**Details** <u>Ethics</u> Ethics approval not stated <u>Setting</u> Not stated <u>Protocol</u> Children received each treatment in a cross-over deisgn <u>Monitoring</u> MII-pH monitoring <u>Outcome measures</u> - Total number of reflux episodes - Number of acid reflux episodes - Number of weakly acidic episodes - Number of weakly alkaline episodes - Number of pH-only reflux - Height of reflux episodes - Reflux index - Number of episodes > 5 minutes in duration <u>Statistical analysis</u> Wilcoxon signed rank test X^2 test Fisher exact test	**Results** Outcome: AAF period, CM period - Median number of reflux episodes, median (25th to 75th centile): 65 (39 to 87.5), 105 (58 to 127.5)(p<0.001) - Acid refluc episodes, median (25th to 75th centile): 31 (9.5 to 44), 34 (14 to 41)(NS) - Reflux index, mean (SD): 3.4 (2.6), 3.6 (2.7)(NS) - Number of episodes lasting > 5 minutes, median (25th to 75th centile): 3 (1 to 3), 2 (1.5 to 2.5)(NS)	**Limitations** - Observational study design

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
the type and physical characteristics of reflux episodes udring 48-hour MII-pH monitoring. **Study dates** Not stated, but recruited over a 12 month period **Source of funding** Not stated					
Full citation Chao,H.C., Vandenplas,Y., Effect of cereal-thickened formula and upright positioning on regurgitation, gastric emptying, and weight gain in infants with regurgitation, Nutrition, 23, 23-28, 2007 **Ref Id** 219358 **Country/ies where the study was carried out** Taiwan **Study type** Randomised controlled trial	**Sample size** • 80 recruited • 18 discontinued (8 group A, 10 group B) due to intolerance with formula • 62 completed study **Characteristics** Characteristic: group A, group B • Age (days): 130.7 (26.5), 129.1 (26.2) **Inclusion criteria** 3 or more episodes of regurgitation/vomiting	**Interventions** - Cereal-thickened regular formula (2.5g of cereal cornstarch added to 3 scoops of Nestle formula)(83.65 kcal) - Regular formula (Nestle formula) plus positional management (67 kcal)	**Details** Setting Outpatient clinic Protocol Randomised by computer to one of the interventions Outcome measurements • Episodes of regurgitation/vomiting as reported by parent • Weight gain Statistical analyses Student's t-test and Wilcoxon signed rank test	**Results** 1-month Outcome: Cornstarch, Regular; mean (SD) • Frequency of regurgitation/vomiting: 2.39 (0.86), 2.84 (0.81) • Weight gain (g): 636.2 (103.4), 577.4 (102.7) 8-weeks • Frequency of regurgitation/vomiting: 1.61 (0.76), 2.38 (0.83) • Weight gain (g): 1261.3 (131.4), 1121.4 (137.2)	**Limitations** • Method randomisation and concealment not described in detail • Compares thickened formula with positional management. • Formula had different nutritional content • 22.5% discontinuation rate

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study Evaluate the clinical effect and the effect on GER as measured by scintigraphy of cereal-thickened formula compared with positional management in the treatment of regurgitation and vomiting. **Study dates** Not stated **Source of funding** Not stated	**Exclusion criteria** - Breast-fed - Any underlying conditions - Intolerant to formulas being used				
Full citation Wenzl,T.G., Schneider,S., Scheele,F., Silny,J., Heimann,G., Skopnik,H., Effects of thickened feeding on gastroesophageal reflux in infants: a placebo-controlled crossover study using intraluminal impedance, Pediatrics, 111, e355-e359, 2003 **Ref Id** 219385 **Country/ies where the**	**Sample size** 14 No dropouts **Characteristics** • Mean age 42 days (+/- 32 days) • 9 females, 5 males **Inclusion criteria** • Recurrent regurgitation (> 5 per day)	**Interventions** Formula with or without 0.4% of carob bean gum. Study phase lasted for 24 hour or 6 feeds Group A: A, B, A, B, A, B Group B: B, A, B, A, B, A	**Details** **Setting** Not stated **Outcome measurements** • Regurgitation score • Number of reflux episodes • Number of regurgitation episodes • Acid reflux episodes • GER height after feed **Method of randomisation and concealment** Randomisation code was computer generated with infant receiving feeds in alternate crossover.	**Results** **Outcome: Formula A, Formula B** Regurgitation score: 0.6, 1.8, $p < 0.003$ Total GER episodes: 535, 647, $p < 0.02$ Number of regurgitation episodes: 15, 68, $p < 0.003$ No regurgitation: 7 of 14, 1 of 14. Primary data presented for reanalysis	**Limitations** Short duration of study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study was carried out Germany **Study type** Randomised controlled trial; crossover **Aim of the study** Evaluate the effect of formula thickened with carob bean gum. **Study dates** Not stated **Source of funding** Grant from START, Medizinische Fakultat Formulas from Milupa	• Aged < 4 months • Body weight > 2000g • Exclusively formula fed **Exclusion criteria** • Suspected food allergy • Gastroenteritis • Other acute infection • Apnoea and/or bradycardia • Regurgitation secondary to other cause Medication influencing oesophageal motility		Formula was prepared by an independent researcher. Blinded allocation to investigator **Monitoring** Impedence and pH monitoring Regurgitation volume and time based on continual monitoring and video-surveillance **Statistical analysis** Paired Wilcoxon test		
Full citation Iacono,G., Vetrano,S., Cataldo,F., Ziino,O., Russo,A., Lorello,D., D'amico,D., Di,Rosa C., Le,Moli C., Di,Prima L., Giannitrapani,L., Cavataio,F., Clinical trial with thickened feeding for treatment of regurgitation in infants, Digestive and Liver Disease, 34, 532-533, 2002	**Sample size** 166 started study 14 from thickened feed group discontinued study **Characteristics** Characeteristic: thickened feed, standard feed Number of infants: 82, 84 Median age: 1.5, 1.5 Sex male: 45, 43	**Interventions** Thickened feed: carob flour (locust bean gum) anti-regurgitation formula for 8 weeks Standard feed: Stndard formula without thickener for 8 weeks Other treatments not mentioned	**Details** Ethics Not stated Setting Six paediatric centres Protocol Randomised to one of interventions Treatment lastest for 8 weeks Measurement at baseline, 4 weeks and 8 weeks. Outcomes Frequency of regurgiation	**Results** Outcome: Thickened feed, Standard feed Infants were asymptomatic: 34%, 14% Discontinued treatment: 14, 4	**Limitations** - Method of randomisation and concealment not described in detail - 14 of 82 infants in thickened feed group discontinued study **Other information** Regurgitation was reduced in both groups from baseline measuresments

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 262162 **Country/ies where the study was carried out** Italy **Study type** Randomised controlled trial **Aim of the study** The clinical usefullness of a thickened formula in the treatment of regurgitation. **Study dates** Not stated **Source of funding** Not stated	**Inclusion criteria** Bottle-fed Frequent regurgiation/vomiting **Exclusion criteria** >4 months of age Breast or mixed feeds Signs of complicated GER Known food alergy		Regurgitation score Timing of regurgitation in relation to feeds and sleep <u>Statistical analysis</u> Wilcoxon rank sum test		

I.7 How effective are antacids compared to placebo in alleviating symptoms of GORD, GOR or other GORD related symptoms (such as heartburn in older children)?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Miller,S., Comparison of the efficacy and safety of a new aluminium-free paediatric alginate preparation and placebo in infants with recurrent gastro-oesophageal reflux, Current Medical Research and Opinion, 15, 160-168, 1999 **Ref Id** 174804 **Country/ies where the study was carried out** UK **Study type** Double blind RCT **Aim of the study** To compare the clinical efficacy and safety of a new aluminium-free formulation of alginate (Gaviscon Infant) with placebo over 14	**Sample size** n=90 randomised, 42 to the alginate group, 48 to the placebo group (35 from alginate group and 33 from placebo group completed the trial) **Characteristics** Age in months, mean (SD) Total: 4 (0.28) Alginate: 3.9 (0.40) Placebo: 4.1 (0.39) Alginate vs placebo: p>0.1 Gender, n/N (%) Total: male - 53/88 (60%), female - 35/88 (40%) Alginate: male - 28/42 (67%), female - 14/42 (33%) Placebo: male - 25/46 (54%), female - 21/46 (46%) Alginate vs placebo: p>0.1 Ethnic origin, n/N (%) Total: white - 85/88 (97%), black - 1/88 (1%), asian - 2/88 (2%) Alginate: white - 40/42 (95%), black - 0/42 (0%), asian - 2/42 (5%) Placebo: white - 45/46	**Interventions** - Subjects were randomised to aluminium-free alginate (Gaviscon Infant, Reckitt & Colman Products Ltd) or placebo (placebo not defined) - Sodium alginate (available as a sachet, containing the active ingredients; sodium alginate (225mg) and magnesium alginate (87.5mg) in a total of 0.65g) or matching placebo were administered with food, dependent on the infant's weight and feeding method on entry. - Bottle-fed infants weighing <4.54kg and those weighing ≥4.54kg were given one sachet in at least 115ml of feed or two sachets in at least 225ml of feed, respectively. - Breast-fed infants weighing <4.54kg	**Details** Consent: parental consent obtained Setting: 25 general practice centres in the UK Sample size calculation: 90% power using the 5% significance level, 40 patients per treatment group were required. 30 evaluable patients in each group resulted in a decrease of power to 80%. Method: - Of the 90 paediatric patients recruited in a general practice setting, 42 were randomised to receive alginate and 48 to receive placebo - Before treatment commenced, investigators assessed the patients demographically for incidence of coexisting disease and concomitant medication, and or duration of vomiting/regurgitation and its severity/frequency in the previous 24 hours - The parents/guardians of the patients were issued with a diary card which they were	**Results** **Cessation (or symptom free days) of overt regurgitation** Reported as at least 10% symptom free days, % Alginate: 31% Placebo: 11% Significantly more patients treated with alginate had at least 10% symptom free days compared with patients receiving placebo: p=0.027 **Reduced frequency of overt regurgitation** 1) Reported as vomiting/regurgitation episodes in the previous 24 hours, median (range) Alginate (n=42): baseline - 8.5 (2 to 50), day 14 - 3.0 (0 to 22) Placebo (n=46): baseline - 7.0 (2 to 36), day 14 - 5.0 (0 to 37) Number of episodes of vomiting/regurgitation significantly lower in alginate group compared to placebo: p = 0.009 2) Reported as mean frequency of vomiting/regurgitation episodes after 14 days	**Limitations** NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials A Selection bias A1 - Was there appropriate randomisation - unclear, method of randomisation not reported A2 - Was there adequate concealment - unclear A3 - Were groups comparable at baseline - yes Level of bias: unclear B Performance bias B1 - Did groups get same level of care - yes B2 - Were participants blinded to treatment allocation- 'double blinded' RCT however details not reported B3 - Were individuals administering care blinded to treatment allocation- 'double blinded' RCT however details not reported Level of bias: low C Attrition bias C1 - Was follow-up equal for both groups - yes C2 - Were groups comparable for dropout - yes C3 - Were groups comparable for missing data - yes Level of bias: low D Detection bias

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days in infants with recurrent GOR **Study dates** April 1994 to October 1995 **Source of funding** Parexel International Ltd and Reckitt & Colman Products Ltd	(98%), black - 1/46 (2%), asian - 0/46 (0%) Alginate vs placebo: p>0.1 <u>Weight in kg, mean (SD)</u> Total: 6.6 (0.17) Alginate: 6.5 (0.25) Placebo: 6.6 (0.23) Alginate vs placebo: p>0.1 <u>Pre-existing medical condition</u> 22% of patients had a pre-existing medical condition upon entry to the study which was comparable between groups **Inclusion criteria** - Pediatric patients aged between 0 and 12 months at the pretreatment assessment - Symptoms consistent with GOR: persistent, unmanageable vomiting/regurgitation or vomiting/regurgitation at least twice daily for the two days prior to the start of the study* *Administration of anti-vomiting/regurgitation medication and use of food thickening agents was not permitted within two days prior to or during the study	and those weighing ≥4.54kg were given one or two sachets, respectively which was mixed to a smooth paste in 5ml of cooled, boiled water diluted with a further 10ml of water administered after each feed using a plastic oral syringe or spoon. - For infants taking solids, two sachets were mixed with water and administered as before. - The dose remained constant throughout the study regardless of any change in weight.	required to complete on a daily basis to record the severity and frequency of symptoms, feeding patterns, compliance with medication, unwanted symptoms and details of concomitant medication - Patients were reassessed after 7 and 14 days - At each assessment, patients were weighed and the diary cards were reviewed - The number and severity of vomiting/regurgitation episodes over the previous 24 hours were noted, together with details of adverse events and any concomitant medication taken <u>Randomisation method:</u> not reported <u>Statistical methods:</u> - number of vomiting/regurgitation episodes: Wilcoxon rank sum test, adjusting for pre-treatment values - severity of vomiting, the investigators and parents/guardians assessments of efficacy: ordinal logistic regression with adjustment for baseline values where recorded - % of symptom free days and area under the curve for change from baseline	Alginate: baseline- 10.2, day 14- 4.5 (SD not reported) Placebo: baseline- 10.6, day 14- 6.2 (SD not reported) The difference in frequency, while favouring alginate, did not quite reach formal statistical significance: p=0.056 **<u>Reflux measured using oesophageal pH-metry</u>** Not reported **<u>Resolution of faltering growth</u>** Not reported **<u>Adverse outcomes, n (%)</u>** Functional diarrhoea: alginate- 6 (14.3), placebo- 5(10.9) Emesis: alginate-1 (2.4), placebo-5 (10.9) Diarrhoea not otherwise specified: alginate- 1 (2.4), placebo- 4 (8.7) Constipation: alginate- 4 (9.5), placebo- 1 (2.2) Colic: alginate- 2 (4.8), placebo- 3 (6.5) Acute nasopharyngitis: alginate- 3 (7.1), placebo- 1 (2.2) No statistically significant differences in the incidence of these adverse events were observed between treatment groups (p>0.1 in all cases) **<u>Parent reported reduction</u>**	D1 - Was follow-up appropriate length - yes D2 - Were outcomes defined precisely - yes D3 - Was a valid and reliable method used to assess outcome - yes D4 - Were investigators blinded to intervention - unclear D5 - Were investigators blinded to confounding factors - unclear Level of bias: low Indirectness Does the study match the review protocol in terms of Population: yes Intervention: yes Outcomes: yes Indirectness: none **Other information** <u>Withdrawals</u> 20 withdrawals from the study (alginate, n=7; placebo, n=13; p>0.2) due primarily to adverse events (alginate, n=4; placebo, n=7) and lack of efficacy (alginate, n=2; placebo, n=3). <u>Compliance</u> 71% and 59% of patients on alginate and placebo, respectively had a compliance of >70%

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	and a record was kept of any medication taken concomitantly **Exclusion criteria** - Known or suspected oesophageal disease - Significant gastrointestinal disease or uncontrolled neurological, cardiac, respiratory, metabolic, hepatic disease or renal impairment - Were more likely to experience excessive water loss (eg: fever, diarrhoea) - Had not yet completed the 37th week of development or weighed less than 2.5kg - Were receiving drugs likely to cause sodium retention - Had previously participated in the present study or were currently participating in any other clinical study - Suspected or known sensitivity to alginates		severity and frequency of vomiting/regurgitation: Wilcoxon rank sum test - adverse events: chi-squared or Fisher's exact test, as appropriate	**in infant distress** Reported as parent/guardian assessment of symptoms, n Alginate Very good + good: 33 Acceptable + poor + very poor: 8 Placebo Very good + good: 21 Acceptable + poor + very poor: 23 Chi squared equals 8.468 with 1 degrees of freedom. The two-tailed P value equals 0.0036 **Improvement in validated reflux questionnaire** Not reported **Parent satisfaction with this intervention** Not reported	
Full citation Buts,J.P., Barudi,C., Otte,J.B., Double-blind controlled study on the efficacy of sodium alginate (Gaviscon) in reducing gastroesophageal reflux assessed by 24 h continuous pH monitoring in infants	**Sample size** n=20, 10 to Gaviscon group and 10 to placebo **Characteristics** Age in months, mean Gaviscon: 21 months Placebo: 35 months Gender, n/N (%)	**Interventions** Gaviscon (alginate) versus placebo	**Details** Consent: parental consent obtained Setting: not reported Sample size calculation: not reported Method: - 20 infants and children with characteristic symptoms of	**Results** **Cessation (or symptom free days) of overt regurgitation** Not reported **Reduced frequency of overt regurgitation** Numbers in each group not reported but authors state: ' After Gaviscon treatment, the number of episodes of	**Limitations** NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials A Selection bias A1 - Was there appropriate randomisation - unclear, method of randomisation not reported A2 - Was there adequate concealment - no, alternate allocation A3 - Were groups comparable at baseline - yes

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and children, European Journal of Pediatrics, 146, 156-158, 1987 **Ref Id** 219342 **Country/ies where the study was carried out** Belgium **Study type** Double blind RCT **Aim of the study** To assess the effect of an alginate compound (Gaviscon) in the treatment of patients with symptomatic reflux **Study dates** Not reported **Source of funding** Not reported	Gaviscon: 4/10 (40%) Placebo: 5/10 (50%) **Inclusion criteria** - Patients with characteristic symptoms of GOR (vomiting, acid regurgitation related to meals and posture, heartburn, recurrent respiratory tract disorders)* *Before the trial, sensitive pH monitoring variables of acid reflux were abnormal in all patients tested. An oesophagram was performed in all patients and revealed GOR in 13 of 20 patients. No oesophagitis was seen on the 14 patients who underwent endoscopy. **Exclusion criteria** - Premature infants - Small for date infants - Patients with severe oesophagitis (stage III and IV according to Belsey) - Renal disease causing sodium retention		GOR were divided at random into 2 groups which were given either Gaviscon or placebo - 24 hour pH probe monitoring was performed in all patients at baseline and after 8 days of treatment - The two preparations were presented in an identical sachet form, lactose being substituted for the alginate in the appropriate coded sachet - Each sachet contained 2g of either alginate or lactose powder - During the trial (8 days), infants received one sachet per 240ml of milk fed and children one sachet dissolved in half a tumbler of water taken after each meal - During the 2nd pH recording, one sachet was given with each milk or orange juice fed (six times per 24 hours) - The parents recorded on a chart the number of times the infants vomited - Electrolyte studies were performed in about one half of the Gaviscon treated patients because of the small quantity of sodium bicarbonate included in the preparation <u>Randomisation method:</u> not reported	regurgitations per day reported by the parents of infants treated was reduced by 3 to 4 times during the trial. Vomiting improved in all cases; in some it ceased completely from 2/3 episodes per day to none, in others, the frequency and volume were decreased'. **<u>Reflux* measured using oesophageal pH-metry</u>** ***A reflux episode was defined as a decrease in the oesophageal pH to <4 for at least 25 seconds** 1. Total number of reflux episodes (24 hour), mean ± SE Before gaviscon - 131.6 ± 29.5, after gaviscon - 56.0 ± 16.8, p<0.05* Before placebo - 87.2 ± 15.5, after placebo - 90.6 ± 14.7, p=NS* 2. Number of reflux episodes greater than 5 minutes, mean ± SE Before gaviscon - 5.5 ± 0.5, after gaviscon - 1.2 ± 0.2, p<0.05* Before placebo - 5.2 ± 0.8, after placebo - 4.6 ± 0.9, p=NS* 3. Percent total reflux, mean ± SE Before gaviscon - 13.4 ± 2.3, after gaviscon - 6.1 ± 0.3, p<0.05*	Level of bias: medium <u>B Performance bias</u> B1 - Did groups get same level of care - yes B2 - Were participants blinded to treatment allocation - yes B3 - Were individuals administering care blinded to treatment allocation - yes Level of bias: low <u>C Attrition bias</u> C1 - Was follow-up equal for both groups - yes C2 - Were groups comparable for dropout - yes, no dropout C3 - Were groups comparable for missing data - yes, no missing data for outcomes measured, however not all patients endoscoped Level of bias: low <u>D Detection bias</u> D1 - Was follow-up appropriate length - yes D2 - Were outcomes defined precisely - yes D3 - Was a valid and reliable method used to assess outcome - no, not all subjects endoscoped D4 - Were investigators blinded to intervention - unclear D5 - Were investigators blinded to confounding factors - unclear Level of bias: unclear Indirectness Does the study match the review protocol in terms of Population: yes Intervention: yes

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			Statistical methods: statistical significance of results was assessed by the unpaired student t-test and the Mann-Whitney U test	Before placebo - 10.4 ± 0.4, after placebo - 10.1 ± 1.4, p=NS* *Probability vs results before treatment **Resolution of faltering growth** Not reported **Adverse outcomes** No adverse effects were observed **Parent reported reduction in infant distress** Not reported **Improvement in validated reflux questionnaire** Not reported **Parent satisfaction with this intervention** Not reported	Outcomes: yes Indirectness: none **Other information** Only 14 patients were endoscoped: none had evidence of oesophagitis Other reflux measures reported in the article (but not specified in the protocol): Euler-Byrne index, mean duration reflux during sleep, number of reflux episodes 2 hour post-cibal, percent reflux time during sleep
Full citation Del,Buono R., Wenzl,T.G., Ball,G., Keady,S., Thomson,M., Effect of Gaviscon Infant on gastro-oesophageal reflux in infants assessed by combined intraluminal impedance/pH, Archives of Disease in Childhood, 90, 460-	**Sample size** n=20 **Characteristics** Age: median - 163.5 days, range: 34-319 Gender: male - 11/20 (55%), female - 9/20 (45%)	**Interventions** Six random administrations (3+3) of Gaviscon Infant* (625mg in 225ml milk) or placebo (mannitol and Solvito N, 625mg in 225ml milk) *Gaviscon Infant consists of sodium and magnesium	**Details** Consent: parental consent obtained Setting: not reported Sample size calculation: not reported Method: - Infants exclusively bottle fed with symptoms clinically suggestive of GOR, underwent 24 hour studies	**Results** **Cessation (or symptom free days) of overt regurgitation** Not reported **Reduced frequency of overt regurgitation** Not reported **Reflux measured using 24 hour studies of intra-oesophageal impedance and dual channel pH**	**Limitations** NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials A Selection bias A1 - Was there appropriate randomisation - unclear, method of randomisation not reported A2 - Was there adequate concealment - yes, identical preparations given to infants A3 - Were groups comparable at baseline - unclear, baseline characteristics not reported

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463, 2005 **Ref Id** 219364 **Country/ies where the study was carried out** UK **Study type** Double blind RCT **Aim of the study** To investigate the influence of Gaviscon infant on GOR in infants using combined pH and intraluminal impedance measurement **Study dates** Not reported **Source of funding** Reckitt Benckiser Healthcare (UK) Ltd, the producers of Gaviscon Infant, funded one of the authors	**Inclusion criteria** - Infants under 12 months of age - Symptoms clinically suggestive of GOR (eg: regurgitation >3x/day any amount or >once/day half the feed) - Over 2000g in weight - Exclusively bottle fed formula milk or expressed breast milk - No signs of acute infection (Patients who were taking acid suppressing or motility agents had therapy stopped at least 3 days (5 days in the case of omeprazole) before beginning the study) **Exclusion criteria** Not reported	alginate and mannitol; it does not contain bicarbonate	of intra-oesophageal 6 channel impedance and dual channel pH monitoring, during which 6 random administrations (3+3) of Gaviscon infant or placebo were given in a double blind fashion - Impedance/pH reflux data were recorded and analysed blindly by one observer Randomisation method: not reported Statistical methods: Wilcoxon signed rank test	**monitoring** 1. Number of reflux events per hour, median (range) Difference (placebo - gaviscon infant): 0.06 (-1.20 to 3.80) p=0.784 **Resolution of faltering growth** Not reported **Adverse outcomes** Not reported **Parent reported reduction in infant distress** Not reported **Improvement in validated reflux questionnaire** Not reported **Parent satisfaction with this intervention** Not reported	Level of bias: unclear B Performance bias B1 - Did groups get same level of care - yes B2 - Were participants blinded to treatment allocation- yes B3 - Were individuals administering care blinded to treatment allocation- yes Level of bias: low C Attrition bias C1 - Was follow-up equal for both groups - yes C2 - Were groups comparable for dropout - unclear C3 - Were groups comparable for missing data - unclear Level of bias: unclear D Detection bias D1 - Was follow-up appropriate length - yes D2 - Were outcomes defined precisely - yes D3 - Was a valid and reliable method used to assess outcome - yes D4 - Were investigators blinded to intervention - yes D5 - Were investigators blinded to confounding factors - yes Level of bias: low Indirectness Does the study match the review protocol in terms of Population: yes Intervention: yes Outcomes: yes Indirectness: none

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Other information Other reflux measures reported in article (but not specified in protocol): number of acid reflux events per hour, number of reflux events in hours 1 or 2, average reflux height, average minimum distal pH, average minimum proximal pH, total acid clearance time per hour
Full citation Forbes,D., Hodgson,M., Hill,R., The effects of gaviscon and metoclopramide in gastroesophageal reflux in children, Journal of Pediatric Gastroenterology and Nutrition, 5, 556-559, 1986 **Ref Id** 234014 **Country/ies where the study was carried out** Australia **Study type** Double blind RCT **Aim of the study** To assess the short-term response, as	**Sample size** n=20, 10 given Alginic acid with antacid and 10 given placebo **Characteristics** Age in months: Alginic acid/antacid group: mean - 71, range - 4 to 168 Placebo: mean - 65, range - 4 to 203 Gender: Not reported Symptoms: Vomiting and/or waterbrush: alginic acid/antacid group - 10/10 (100%), placebo - 10/10 (100%) Failure to thrive: alginic acid/antacid group - 1/10 (10%), placebo - 2/10 (20%) Chest disease: alginic acid/antacid group - 5/10 (50%), placebo - 6/10 (60%) Esophageal symptoms: alginic acid/antacid group -	**Interventions** Alginic acid with antacid (Gaviscon Infant Liquid*) vs placebo* (saline 0.9%) *The drugs were administered as recommended in their accompanying manufacturers' instructions. Gaviscon Infant Liquid was given as 10ml every 6 hours for infants and 20 ml every 6 hours for older children. The placebo was given prior to meals in a 1ml oral dose every 8 hours.	**Details** Consent: informed parental consent obtained Setting: Gastroenterology service of the Princess Margaret Hospital for Children Sample size calculation: not reported Method: - Patients with abnormal numbers of reflux episodes and abnormal duration of reflux (as determined by 24 hour esophageal pH monitoring at baseline) were randomised to receive metoclopramide, alginic acid with antacid (Gaviscon Infant Liquid) or a placebo (saline 0.9%) during a second consecutive 24 hour period of esophageal pH monitoring - The drugs were administered as described above - Children were free to move	**Results** **Cessation (or symptom free days) of overt regurgitation** Not reported **Reduced frequency of overt regurgitation** Not reported **Reflux measured using oesophageal pH-metry or impedance monitoring** 1. Number of episodes of GER (esophageal pH <4), mean ± SE Alginic acid/antacid group - before treatment 87 ± 17, after treatment 81 ± 23 Placebo - before treatment 70 ± 13.5, after treatment 49 ± 11 P=NS 2. Total duration of acid reflux in minutes, mean ± SE Alginic acid/antacid group - before treatment 90 ± 39, after treatment 74 ± 39	**Limitations** NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials A Selection bias A1 - Was there appropriate randomisation - unclear, method of randomisation not reported A2 - Was there adequate concealment - unclear A3 - Were groups comparable at baseline - yes Level of bias: unclear B Performance bias B1 - Did groups get same level of care - yes B2 - Were participants blinded to treatment allocation - yes B3 - Were individuals administering care blinded to treatment allocation - yes Level of bias: low C Attrition bias C1 - Was follow-up equal for both groups - yes C2 - Were groups comparable for dropout - yes C3 - Were groups comparable for

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measured by 24 hour esophageal pH monitoring, to metoclopramide or liquid Gaviscon in a group of referred pediatric patients with gastroesophageal reflux **Study dates** Not reported **Source of funding** Not reported	4/10 (40%), placebo - 3/10 (30%) **Inclusion criteria** - Infants, children and adolescents with GER who were referred by their pediatricians to the Gastroenterology Service for esophageal pH monitoring* *7 out of a total of 30 subjects (10 in the alginic/antacid group, 10 in the placebo group and 10 in the metoclopramide group) had endoscopy and biopsy evidence of esophagitis, and one of these had a Barrett's esophagus. The remaining patients with esophageal symptoms had pain, which was believed to emanate from the esophagus, but they had not undergone endoscopy. **Exclusion criteria** - Patients with cerebral palsy or other neuromotor diseases		around their bed, which was maintained in a horizontal position - No standard nursing position was defined for infants - All infants were fed standard hospital diets at regular meal times - All recordings were analysed blindly by one observer Randomisation method: not reported Statistical methods: The control and treatment data for each group were compared using the Wilcoxon signed rank test	Placebo - before treatment 120 ± 10, after treatment 96 ± 11 P=NS **Resolution of faltering growth** Not reported **Adverse outcomes** No side effects attributable to the drugs were observed **Parent reported reduction in infant distress** Not reported **Improvement in validated reflux questionnaire** Not reported **Parent satisfaction with this intervention** Not reported	missing data - yes Level of bias: unclear D Detection bias D1 - Was follow-up appropriate length - yes D2 - Were outcomes defined precisely - yes D3 - Was a valid and reliable method used to assess outcome - no, not all subjects endoscoped D4 - Were investigators blinded to intervention - yes D5 - Were investigators blinded to confounding factors - unclear Level of bias: low Indirectness Does the study match the review protocol in terms of Population: yes Intervention: yes Outcomes: yes Indirectness: none **Other information** - The data for the metoclopramide group has not been considered as it is not the intervention of interest for this review question

I.8 Effectiveness of medical management (H_2RAs, PPIs and prokinetics) in GOR or GORD

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Cucchiara,S., Gobio-Casali,L., Balli,F., Magazzu,G., Staiano,A., Astolfi,R., Amarri,S., Conti-Nibali,S., Guandalini,S., Cimetidine treatment of reflux esophagitis in children: an Italian multicentric study, Journal of Pediatric Gastroenterology and Nutrition, 8, 150-156, 1989 **Ref Id** 219192 **Country/ies where the study was carried out** Italy **Study type** Randomised placebo-controlled trial **Aim of the study** Assess in a double-blind trial the place of pharmacologic therapy in the treatment of children with moderate to severe peptic oesophagitis in	**Sample size** 37 entered study 32 completed study: 17 cimetidine, 15 placebo **Characteristics** <u>Characteristic: Cimetidine; Placebo</u> - Number of cases: 17; 15 - Age, months (mean (SD)): 21.7 (37.65); 29.03 (39.73) - Age range: 1 month to 9.5 years; 2 months to 14 years - Vomitting/regurgitation, no.(%): 13(76.47); 14(93.3) - Heartburn, dysphagia, no.(%): 5(29.41); 5(33.3) - Hematemesis, no(%): 3(17.64); 2(13.3) - Pneumonia, apnea, no.(%): 3(17.64); 2(13.3) **Inclusion criteria** - Established peptic reflux esophagitis - Diagnosis of GER based on prolonged (18-24 hour) intraesophageal pH monitoring after excluding infectious, neurologic, and metabolic disorders - Reflux defined as: a drop of the distal esophageal pH <4.00 for at least 20 seconds	**Interventions** Cimetidine - 30 to 40 mg/kg/day three time a day after meals for 12 weeks Placebo - 30 to 40 mg/kg/day three time a day after meals for 12 weeks - All patients received intensive postural therapy - Both drugs administered in presentations identical in taste and appearance - Children were given their daily regular feedings as desired - No other drug treatment for reflux was used during trial period	**Details** <u>Ethics</u> - Study approval by Ethical Committee at each institution - Parents gave informed consent <u>Setting</u> - Not stated - Outpatients entered the study <u>Randomisation and conealment</u> - Histologic assessment was carried out by histopathologists who were unaware of the endoscopic appearance or treatment status - Randomisation not described <u>Method of monitoring</u> - 24-hour pH monitoring: GORDdefined as pH < 4 for at least 3% of time - Endoscopic and histologic examination: oesophagitis based on number of oeosninophils or neutrophils - Diary cards completed by parents recording symptoms (clinical scoring system based on frequency of regurgitation, episodes of asthma or pneumonia, apneoa, heartburn,	**Results** Outcome: Cimetidine; Placebo Number 17; 15 <u>Clinical score</u> Pre trial: 14.64 (+/- 3.74); 13.4 (+/- 3.75) Post trial: 5.0 (+/- 4.36); 9.46 (+/- 4.86) <u>Histological score</u> Pre trial: 6.35 (+/- 2.78); 6.80 (+/- 2.88) Post trial:1.6 (+/- 2.43); 5.43 (+/- 3.81) <u>Oeosophagitis improved or healed</u>: 16; 6 - Mild or moderate improved or healed: 9 of 9; 4 of 7 - Severe: 7 of 8; 2 of 8 - Nine cimetidine patients had mild or moderate esophagitis, all of them healed and did not show any macroscopic or histological sign of esophagitis. - Seven placebo patients had mild or moderate esophagitis, four (57.14%) healed or had improved conditions ($p<0.05$), and the conditions of three remain unchanged. - Eight cimetidine and eight placebo patients had severe esophagitis. - Seven cimetidine (87.5%) and two placebo patients (25%) were cured or had improved	**Limitations** - Method of randomisation and allocation concealment not explained in detail - Five patients failed to complete the study (treatment group not reported) - Exclusion criteria not explained - Number of patients who failed to meet inclusion criteria not reported **Other information** - Scoring system for symptoms or physical signs for esophagitis assessed by histological findings described in table 1 - GER abnormal if the total exposure acid time for 24 hours >3% - Esophagitis histologically classified as mild when 1 to 19 eosinophils or 4 to 19 neutrophils per high power field were observed, as moderate when ≥20 eosinophils or ≥20neutophils per high power field were seen, and severe

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addition to posture adjustment and thickened feedings. **Study dates** Not stated **Source of funding** Not stated	**Exclusion criteria** None specified		weight/height ratio, oesophagitis, hematemesis) Outcomes: - Clinical score (based on vomitting/regurgitations, pneumonia/asthma, apnea, hematemesis, heartburn, weight/height ratio, esophagitis) - Histological score Statistical methods Student's t-test, chi2 and Fisher's exact test	conditions (p<0.05), whereas the condition of one cimetidine patient (12.5%) and six placebo patients (75%) remained unchanged or worsened (p<0.05). - The patients whose conditions were judged as improved or healed after a further month of treatment, however one cimetidine showed symptomatic and endoscopic relapse 4 months later. - Among the 10 patients with unchanged or worsened conditions (9 placebo, 1 cimetidine), nine were subsequently treated with ranitidine hydrochloride, and one was treated with intensive administration of liquid magnesium hydroxide and aluminium hydroxide for 12 weeks. - No advserse events reported.	when there was also evidence of mucosal ulceration
Full citation Carroccio,A., Iacono,G., Montalto,G., Cavataio,F., Soresi,M., Notarbartolo,A., Domperidone plus magnesium hydroxide and aluminum hydroxide: a valid therapy in children with gastroesophageal reflux. A double-blind randomized study versus	**Sample size** 80 children across 4 groups **Characteristics** All children in study Age range: 1 to 18 months, median 4.5 months Sex: 45 males, 35 females Group A: - 11 males, 9 fmales	**Interventions** Groups A & B were combination therapies. The results for these are not reported Group C: Domperidone (0.3 mg/kg/dose 15 minutes before meal) and placebo, administered 1 and 3 hours after meals, for 8 weeks Group D: Received two different preparations of	**Details** Ethics Not stated Setting Not stated Randomisation and concealment - Stratification to ensure balanced groups for age (<12 months and =>12 months) and total reflux	**Results** No statistcial differences between groups at baseline. Outcome at 8 weeks: Group C - domperidone; Group D - placebo Median (range) Reflux time Pre trial: 10 (7 to 41); 9 (7 to 41) Post trial: 8 (2 to 35); 9 (3 to 40) Number of reflux episodes	**Limitations** - Method of concealment not described in detail - Jolley score subjective outcome measure and not described - Number of patients cured, improved or unchanged after therapy is an unclear meaure of outcome

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
placebo, Scandinavian Journal of Gastroenterology, 29, 300-304, 1994 **Ref Id** 219339 **Country/ies where the study was carried out** Italy **Study type** Randomised controlled trial **Aim of the study** Evaluate the efficacy of treatment with the comcination of treatments: a) domeridone-Gaviscon and b) domperidone_Maalox **Study dates** Not stated **Source of funding** Not stated	- Age range 1 to 18 months, median 5 months - 18 cases of first-degree esophagitis and 2 of second-degree esophagitis Group B: - 12 males, 8 females - Age range 1 to 17 months, median 4 months - 17 cases of first-degree esophagitis and 3 of second-degree esophagitis Group C: - 11 males, 9 females - Age range 1 to 16 months, median 5 months - 16 cases of first-degree esophagitis and 4 of second-degree esophagitis Group D: - 11 males, 9 females - Age range 1 to 16 months, median 4 months - 18 cases of first-degree esophagitis and 2 of second-degree esophagitis **Inclusion criteria** GER confirmed by presence of at least 2 reflux episodes during fluoroscopy and 24-hour pH monitoring (RI >5.2%)	placebo administered 1 and 3 hours after meals, for 8 weeks Additional treatments: fractionated feeding, thickened milk formulas for unweaned infants and positional management	time <10% or => 10% - Block randomisation - Assessment of results was blinded Method of monitoring - 24-hour pH monitoring at baseline and 8 weeks (most of the children spent the monitoring period at home) - Reflux time - Number of reflux episodes - Duration of longest reflux (minutes) - Number of reflux episode > 5 minutes - Jolley score (also used by Iacono et al) Statistical analysis - Wilcoxon rank sum to compare pH data - Mann-Whitney U test to compare across groups - Chi-squared to compare percentages of patients cured, improved or unchanged Follow-up Monthly for a period of 6 months after treatment	Pre trial: 59 (31 to 161); 65 (28 to 121) Post trial: 48.5 (2 to 181), 68 (38 to 130) Duration of the longest reflux episode (minutes) Pre trial: 30.5 (4 to 150); 30.5 (10 to 92) Post trial: 16 (2 to 51); 33.5 (8 to 103) Number of reflux episodes > 5 minutes Pre trial: 6.5 (0 to 18); 6.5 (1 to 18) Post trial: 7.5 (0 to 16); 6 (1 to 20) Jolley score Pre trial: 310 (131 to 794); 315 (125 to 782) Post trial: 126 (15 to 540); 243.5 (36 to 802) Number of patients cured, improved or unchanged after therapy Cured: 9 out of 20; 7 out of 20 Improved: 7 out of 20; 3 out of 20 Unchanged: 4 out of 20; 10 out of 20 - In group C a significant reduction in the number of reflux episodes (p<0.009) and in the Jolley score (p<0.04) - In group D a significant reduction only in the duration of the longest reflux episode	**Other information** - All the patients who were not cured at the end of the trial were treated with a combined therapy of cispride and H2 blockers, and there was complete regression of symptoms <3 months after the beginning of this treatment in 36 patients - The four subjects who did not respond to this treatment were referred to a specialist for a posssibe surgical intervention - First degree esophagitis characterised by normal endoscopic findings or erythema of the mucosa, with a histological finding of lengthening of the papillae, an increased thickness of the lamina propria, and an infiltration of <20 eosinophils or neutrophils per microscopic field; a cell filtration of >20 elements per field considered to be second degree

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	Exclusion criteria - Infectious, neurologic and metabolic diseases - Pyloric stenosis			(p<0.05)	esophagitis; and endoscopic and histological findings of erosions and/or ulcers characteried third and fourth degree esophagitis respectively
Full citation Moore,D.J., Tao,B.S., Lines,D.R., Hirte,C., Heddle,M.L., Davidson,G.P., Double-blind placebo-controlled trial of omeprazole in irritable infants with gastroesophageal reflux, Journal of Pediatrics, 143, 219-223, 2003 **Ref Id** 245898 **Country/ies where the study was carried out** Australia **Study type** Randomised, double-blind, placebo controlled cross-over trial **Aim of the study**	**Sample size** - 64 Assesses for inclusion: presenting with frequent spilling and crying at levels that made the parents seek help - 34 Entered study, 4 withdrawn by parents during the first 2-week treatment period because of persistent crying - 30 Completed study: 15 placebo, 15 omeprazole **Characteristics** - Age, months: median 4.8, range 3 to 10.2, mean 5.4±2.1 - 23 boys, 7 girls - Esophageal acid exposure >5% (n=22) and/or abnormal esophageal histology (n=15) - No infant had a history of hematemesis or melena **Inclusion criteria** - Recruited after referrals from pediatricians, general practioners and postnatal clinics	**Interventions** - Omeprazole (infants from 5 to 10kg were given 10mg daily and >10 kg were given 10 mg twice daily) for 2 weeks - Placebo identical appearance to omeprazole for 2 weeks (supplied by AstraZeneca) - The omeprazole and placebo were presented in a capsule as microspheres - The contents of each capsule was emptied into a teaspoon of applesauce and administered to the infant - All infants received emperical pharmacologic treatment for GER and irratibility, which included cisapride 87%, H2 receptor antagonist 73%, antacid 67% and thickening agent 20%. - None of the infants had been given an empircal trial of proton pump	**Details** <u>Ethics</u> Ethical approval and informed conent <u>Setting</u> Paediatric unit, 4 week crossover trial completed at home <u>Randomisation and concealment</u> - Double-blind, randomised, cross-over at 2 weeks - The patient code indicating the order of treatment was broken at the compltion of the study - Parents blinded to theraputic agents <u>Method of monitoring and measurement</u> - Parent diary of child behaviour (as described by Barr et al.) recording crying/fussing, kept for ≥5 days at baseline and during the second week of each treatment period	**Results** Omeprazole; placebo (mean (SD)) <u>Reflux index</u> Basline: 9.9 (5.8); 7.2 (6.0) At end of period 1: 1.0 (1.3); 5.3 (4.9) Change in RI: -8.9 (5.6); -1.9 (20); p<0.001 <u>Cry/fuss minutes per 24 hours</u> - Baseline 246 (105); 287 (132) - Period 1: 203 (113); 204 (87) - Baseline versus period 1, p=0.40 - Period 2: 179 (129); 198 (115) - Baseline versus period 2, p=0.008 <u>VAS for irritability</u> - Baseline: 7.1 (1.4); 6.6 (1.7) - Period 1: 5.9 (2.6); 6.0 (2.1) - Period 2: 4.0 (3.3); 5.7 (2.2) - Baseline versus period 2, p=0.008 No adverse events encountered	**Limitations** - No washout period between treatments - Method of randomisation and blinding not explained in detail - Reliability of parent diaries - VAS is a subjective scoring measure - Characteristics not reported per treatment group **Other information** - None of the 64 infants had endoscopic changes of erosive or ulcerative esophagitis; 29 had normal endoscopic findings in the distal esophagus, whereas 35 demonstrated loss of vascular pattern and/or an increase in friablity after biopsy

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Investigated the role of omeprazole in irritable infants with significant GER **Study dates** Not stated **Source of funding** - Gunn Medical Research foundation and Channel 7 Children's Research Foundation - Omeprazole and placebo capsules supplied free of charge by AstraZeneca	- Aged 3 to 12 months - Significant GER: RI of >5% Or Esophagitis based on biopsy - intra-epithelial oeosinophils or any two of the following: basal cell layer thickness of >20% of total epithelial thickness, papillary length >60% of total epithelial thickness, and 20% lymphocytes in at least one high power field. **Exclusion criteria** Medical or sugical conditions other than GER	inhibitor before recruitment	- 10cm VAS of parents assessment of child irratibility at baseline and during each treatment period - 24 hour pH monitoring at baseline and at 2 weeks (at point of cross-over) but not at 4 weeks Statistical analysis - A sample size of 20 infants to detect an improvement in cry/fuss time between omeprazole and placebo of 50%, two sided α=0.05, power=80% - Mann-Whitney U test		- 15 met the endoscopic biopsy criteria, 22 met the esophageal acid exposure criteria, and 7 met both criteria - Cry/fuss score and VAS compared infants with RI>5% with those with RI<5%, and compared infants with RI>10% with those with RI<10%, no signficicant difference was seen at baseline or while taking either omeprazole or placebo
Full citation Omari,T.I., Haslam,R.R., Lundborg,P., Davidson,G.P., Effect of omeprazole on acid gastroesophageal reflux and gastric acidity in preterm infants with pathological acid reflux, Journal of Pediatric Gastroenterology and Nutrition, 44, 41-44, 2007 **Ref Id**	**Sample size** 10 **Characteristics** - Mean postmenstrual age 36.1 (+/- 0.7) weeks (range 34 to 40 weeks) - Mean weight 2217g (+/- 112) (range 1810 to 2700) **Inclusion criteria** - Symptoms suggestive of GERD (feeding problems, vomiting,	**Interventions** - Either 5mg/ml omeprazole or sterile water - To administer the drug/placebo, a volume of stock equivalent to 0.7 mg/kg omeprazole was added to 2mL/kg of an antacid solution (Mylanta) and the mixture was gavaged via a nasogastric tube - Antacid solution used to stop denaturing of PPI by gastric acid - Drug dosing ocurred on	**Details** Ethics - Study approved by the Ethics Committee of Women and Children's Hospital - Informed consent obtained before each study Setting Neonatal Unit of the Women's and Children's Hospital Randomisation and concealment Drug prepared and dispensed by pharmacy	**Results** Outcome: placebo week; omeprazole week Esophageal pH mean (SEM) - Number of acid GER: 119.4 (20.9); 59.6 (26.7), p<0.05 - Number of acid GER > 5 minutes: 8.0 (2.1); 3.0 (2.0), p<0.01 - Longest acid GER, minutes: 48.6 (10.1); 16.3 (8.0), p<0.01 - % time pH < 4: 19.0 (4.5); 4.9 (3.4), p<0.01 Gastric pH mean (SEM) % time pH < 4: 53.8 (6.8); 13.9	**Limitations** - Small sample size - Statistical analysis not described - Randomisation and blinding unclear - Number of patients who did not meet the inclusion criteria not reported **Other information** Blood biochemistry and blood picture also reported (table 1)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
219368 **Country/ies where the study was carried out** Australia **Study type** Randomised, double-blind, placebo controlled crossover trial **Aim of the study** Determine the effect of 0.7 mg/kg/day omeprazole on gastric acidity and GER in premature infants with reflux symtoms and pathological acid reflux on 24 hour pH probe. **Study dates** Not stated **Source of funding** - Per Lundborg is an employee of and shareholder in AstraZeneca Ltd, the manufacturer of omeprazole - Thank AstraZeneca R&D Molndal for assistance with	irritability, apneoa and weight loss) - Not responded to conservative therapy (feed thickeners, postural changes, antacids) - 24-hour pH monitoring confirming RI > 5 % (% time pH <4) **Exclusion criteria** - <32 weeks post menstrual age - Required CPAP or ventilation - Acute illness (eg necrotizing entercolitis) - Neurological disease (eg intraventricular hemorrhage grade 3/4) - Heptic or renal impairment - Bone marrow abnormalities	the morning of each day just before the scheduled feeding time - After enrollment, the infants were given a 1 week regimen of omeprazole or placebo (days 1-7), the alternative treatment was given for the second week (days 8-14)	according to a randomisation schedule determined using a random number generator <u>Method of monitoring</u> - 24 hour pH monitoring at 7 and 14 days (crossover and end of study) - Blood samples taken on days 6 and 13, 2 hours after administration of the drug - GER symptom assessment chart recording feeding times, frequency of vomitting, apnea, choking and behavioual changes <u>Statistical analysis</u> Paired t-test.	(5.1), p<0.0005 <u>Symptom frequency, no. events, (median (IQR))</u> - Vomiting 8.5 (7 to 22.8); 6.5 (3 to 14.3) - Behavioural changes 17 (8.3 to 27.8); 16.5 (7.3 to 30.1) - Apnea 0.4 (0 to 1.5); 1 (0 to 1.8) - Bradcycardia 7.5 (1.3 to 17.3); 6.5 (3 to 16) - Choking 0 (0 to 1); 0 (0 to 1.8) No serious adverse events encountered	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
performing plasma omeprazole assays					
Full citation Bines,J.E., Quinlan,J.E., Treves,S., Kleinman,R.E., Winter,H.S., Efficacy of domperidone in infants and children with gastroesophageal reflux, Journal of Pediatric Gastroenterology and Nutrition, 14, 400-405, 1992 **Ref Id** 219394 **Country/ies where the study was carried out** USA **Study type** A double-blind randomised controlled study **Aim of the study** Define the therapeutic efficacy of domperidone in infants and children with GORD who have not responded to standard non-pharmacological therapy.	**Sample size** - 17 eligible and randomised: domperidone 8, placebo 9 - 2 pH monitoring was not successful, 15 analysed - 12 open label trial (phase 2) **Characteristics** <u>Characteristic: domperidone; placebo</u> - Age, years (mean (range)): 3.6 (0.5 to 11.3); 2.4 (0.8 to 7.2) - Sex, male: 6; 6 - Underlying disease: Mental retardation: 2; 3 Cystic fibrosis: 1; 1 - Barium swallow demonstrated a normal gastric outlet in all 17 - 7 out of 15 undergoing esophagogastroduodenscopy had histological evidence of active esophagitis demonstrated by intraepithlial eosinophils and/or basal zone hyperplasia - No children had evidence of Barrett's esophagus **Inclusion criteria** - Between 5 months and 12 years of age - Gastroesophageal reflux confirmed on 17 to 24-hour	**Interventions** <u>Oral domperidone</u> (0.6 mg/kg) 30 minutes before each meal (three times a day) and at bedtime for 4 weeks <u>Placebo</u> (not described) 30 minutes before meal (three times a day) and at bedtime for 4 weeks	**Details** <u>Ethics</u> Consent obtained in accordance with approval by the Committee on Clinical Investigation Children's Hospital, Boston <u>Setting</u> Not stated <u>Randomisation:</u> Double-blind randomisation (no further information provided). <u>Method of assessment:</u> - Daily diary completed by parents on symptoms and severity - Patients evaluated at 2 week intervals - pH mintoring for 8 to 12 hours and gastric emptying scans at 4 weeks - Adverse events - Global evaluation of efficacy by investigator and parents at 4 weeks <u>Statistical analysis</u> Not stated	**Results** Outcome: Domperidone N=7; Placebo N=8 pH probe (<2h, mean%) <u>Total episodes</u> Baseline: 69; **16** Week 4: 26; 28: p < 0.001 <u>Longest episode</u> Baseline: 14.3; 21.5 Week 4: 12.6; 20.9: p=NS <u>% time pH < 4</u> Baseline: 15.9; 15.2 Week 4: 11.8; 15.9: p=NS <u>Acid clearance</u> Baseline: 0.22; 0.58 Week 4: 0.61; 0.83: p=NS <u>Gastric emptying scan (mean% emptied after 1 hour)</u> Baseline: 64.5; 47.5 Week 4: 49.6; 33.8: p=NS <u>Adverse events</u>: - Diarrhea: 4; 2 - No reports of adverse central nervous system effects	**Limitations** - Method of randomisation and concealment not described - Statistical methods not described - Number of patients who did not meet the inclusion criteria not reported - Small sample size, <10 per group - One patient from each group lost to follow-up **Other information** - Following the double-blind phase of the trial and open-phase trial of continued treatment with domperidone was undertaken. Results from this are not reported - Weight and height Z scores also reported, no significant improvement in weight gain or height was noted after 4 weeks therapy with domperidone compared with placebo - One patient

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Not stated **Source of funding** Supported by a grant from the Janssen Research Foundation	overnight pH probe recording (at least one episode of acid reflux <4 lasting >4 minutes) - Not responding to non-pharmacological treatment (not specified) **Exclusion criteria** - Specific organic lesions that could cause symptoms - Illness that would interfere with assessments - Using medications including bethanechol, metoclopramide, H2-blockers, antiemetics, spasmolytics, anticholinergics, neuroleptics, or tranquilizers				developed transient neutropenia to 306/mm³ after 8 weeks of domperidone therapy in the setting of a probable intercurrent viral infection
Full citation Winter,H., Gunasekaran,T., Tolia,V., Gottrand,F., Barker,P.N., Illueca,M., Esomeprazole for the treatment of GERD in infants ages 1-11 months, Journal of Pediatric Gastroenterology and Nutrition, 55, 14-20, 2012 **Ref Id** 219445 **Country/ies where the study was carried out**	**Sample size** - 98 enrolled in 2-week open-phase - 18 discontinued from open label phase: 9 lack of theraputic response, 5 AEs, 4 voluntary discontinuation - 80 entered 4-weel double-blind phase: 39 esomeprazole, 41 placebo - 37 completed esomeprazole arm; 40 completed placebo arm. **Characteristics** <u>Characteristic: Esomeprazole; Placebo</u> - Mean (SD) age months: 4.9	**Interventions** - After the open-label phase, infants were randomised 1:1 to double-blind treatment with esomeprazole (at the open-label dose) or placebo for up to 4 weeks - Esomeprazole (Nexium oral capsules; AstraZeneca LP) one daily orally (2.5, 5 or 10 mg capsules for infants weighing 3-5 kg, >5-7.5 kg, >7.5 to 12 kg, respectively) - Parents/guardians were provided with sachets containing an inactive granulate (forms viscous suspension when added	**Details** <u>Ethics</u> - Declaration of Helsiniki - Approval from appropriate institutional review boards for participating centres - Written informed consent of parent/guardian obtained before initiation of study <u>Setting</u> 33 centers across USA, France, Germany and Poland <u>Randomisation and concealment</u> - Initial 2-week open phase trial with all children receiving esomeprazole - If child responded to	**Results** Outcome: esomeprazole; placebo <u>Discontinued owing to worsening symptoms or symptoms worsened:</u> 15 of 39 (38.5%); 20 of 41 (48.8%) Hazard Ratio 0.69 (0.35 to 1.35), p = 0.28 <u>Mean (SD) change from baseline in symptom score during double-blind phase</u> N=37; N=40 - Vomiting/regurgitation: 0.04 (0.56); 0.09 (0.61), NS - Irritability: 0.06 (0.58); 0.19 (0.59), NS - Supraeophageal/respiratory	**Limitations** - Two methods of randomisation are outlined, plus stratification, it is unclear which was used - 33 centers involved in study, but no reporting of recruitment - Blinding unclear - Placebo not described **Other information** - Figure 4 displays factors of clinical importance in time to discontinuation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
33 centers in USA, France, Germany and Poland **Study type** Multicenter randomised, double-blind, placebo controlled trial **Aim of the study** Evaluate the efficacy and safety of esomeprazole in infants aged 1 to 11 months with GERD **Study dates** April 2007 to June 2008 **Source of funding** AstraZeneca LP	(2.6); 4.9 (3.2) - Age range: 1 to 11; 1 to 11 - Boys, n (%): 30 (76.9); 27 (65.9) - Mean (range) dose, mg/kg: 0.86 (0.51 to 1.28); 0.92 (0.50 to 1.33) **Inclusion criteria** - Aged 1 to 11 months - Clinical disgnosis of suspected GERD based on symptoms, endoscopically proven GERD, or an investigator-determined diagnosis of GERD based on the patients history, physical examination, laboratory test results, or findings from disgnostic tests - Patients were required to have >1 of the symptoms of GERD (vomitting/regurgitation, irritability, supraesophageal manifistations of GERD [cough, wheezing and/or stridor, labored breathing], respiratory symptoms triggered by feeding, feeding difficulties [food refusal, gagging/choking, hiccups for >1 hour/day]) at least 2 times per week in a 4 week period - Patients with supraesophageal manifestations of GERD were included if they presented with a clinical picture consistent with GERD - Failed non-pharmaceutical management of GERD (thickened feeds, elimination diet and sleep position) - Eligible for double blind phase	to water) and were instructed to dissolve the contents into 5ml of water and to add the contents of the esomeprazole capsule - The resulting suspension was administered to the infant by syringe or spoon 30 to 60 minutes before feeding - If an infant was unable to tolerate the suspension, then the contents of the drug or placebo capsule could be mixed into applesauce - Maalox liquid or age-appropriate non-bismuth containing liquid antacid was allowed as rescue medication - Patients were discontinued from the study if PGA scored of GERD symptoms worsened by at least 1 category compared with baseline observation	treatment they could enter double blind phase - Randomised 1:1 using computer-generated random number - Randomised in sequential blocks and stratified by weight (3 to 5kg, >5 to 7.5 kg, >7.5 to 12 kg) <u>Method of monitoring</u> - Questions used in the interactive voice response system (IVRS) assessment of GERD symptoms were based on the validated Orenstein's Infant Gastroesophageal Reflux Questionnaire. - IVRS used to capture patients' daily symptoms and use of rescue medications during the previous 24 hour period - The PGA assessed GERD symptoms as none, mild, moderate, or severe during the previous 7 day period based on the severity of symptoms reported by in the IVRS <u>Outcome measures</u> - Discontinuation owing to worsening symptoms - Time to discontinuation of treatment - Proportion of patients achiving treatment success - Symptoms based on I-GERQ including	disturbances: 0.12 (0.48); 0.03 (0.58), NS - Feeding difficulties: 0.09 (0.48); 0.10 (0.61), NS <u>Adverse events</u>: - 23 of 39 (59%); 27 of 41 (66%), NS - Leading to discontinuation: 2; 0 - Two patients who experienced a treatment-related AE in the open-label phase continued to experience the AE during double-blind treatment, tachypnea in a patient receiving esomeprazole, alanine aminotransferase increase in a patient receiving placebo - Respiratory tract infection: 6 of 39 (15.4%); 4 of 41 (9.8%) - Other common AEs in the esomerprazole group included pyrexia (n=5, 12.8%), rhinitis (n=4, 10.3%), diarrhea (n=4, 10.3%) and nasopharyngitis (n=4, 10.3%) - Other common AEs in the placebo group include cough (n=4, 9.8%), pyrexia (n=3, 7.3%), rhinitis (n=3, 7.3%) and nasopharyngitis (n=3, 7.3%)	- Mean symptom score during open-label phase also reported (table 2) - More infants in the placebo 17 of 41 (41.5%) than in the esomeprazole group 10 of 39 (25.6%) discontinued from the study - The most common reason for discontinuation was lack of theraputic response (placebo 17, esomeprazole 8) - Two patients in the esomeprazole group discontinued because of AEs during the double-blind treatment, but because both patients had worsening PGA scores at the time of discontinuation, they were included in the primary analysis as discontinuing owing to symptom worsening - In addition to the 27 randomised patients who discontinued from the study, an additional 8 patients (esomeprazole 5, placebo 3) who completed the study were included in the primary analysis as worsening because

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	of study if: improvement in physician global assessment (PGA) scores of GERD symptoms in at least 1 category during the open-label phase compared with baseline assessment and no indication of severe symptoms that would preclude use of placebo and require medical intervnetion. - PGA assessed symptoms as none, mild, moderate or severe during the pervious 7 days based symptoms reported by parents based on questions included in the I-GERQ questionnaire **Exclusion criteria** - Used PPIs within 7 days - Used over-the-counter treatments for GERD symptoms (eg histamine-2 receptor antagonists, prokinetics and bismuth-containing antacids) within 24 hours of open label study starting - Active GI bleeding, apnea, allergic gastroenteropathies, oesinophilic gastroenteritis, bleeding disorders, pyloric stenosis, active seizure disorders, acute pancreatitis or meningitis		vomiting/regurgitation, irritability, supraeophageal and respiratory disturbances and feeding difficulties <u>Statistical analysis</u> - Sample size was calculated based on the assumpion of an 80% success rate with esomeprazole treatment and 40% success rate with placebo treatment, 38 patients per treatment group would provide >90% power to detect this difference at a two-sided α=0.05 using the Fischer exact test, an estimated 100 patients would need to be enrolled to obtain 76 patients eligible for randomisation - Intention to treat analysis - Cox proportional hazard model used for time to discontinuation - Kaplan Meier estimates for time to discontinuation owing to symptom worsening - Chi squared test used to assess proportion of treatment successes - Additional post-hoc analysis based on sub-groups - PGA analysed using Cochran-Mantel-Haenszel statistic		their PGA scores had worsened at the final visit

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Orenstein,S.R., Hassall,E., Furmaga-Jablonska,W., Atkinson,S., Raanan,M., Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease, Journal of Pediatrics, 154, 514-520, 2009 **Ref Id** 219736 **Country/ies where the study was carried out** USA & Poland **Study type** Multicenter, randomised, double-blind placebo-controlled parallel group trial **Aim of the study** To assess the efficacy and safety of lansoprazole in treating infants with symptoms attributed to GERD that	**Sample size** - 216 screened for inclusion - 54 not randomised: 17 did not meet criteria, withdrew consent or lost to follow-up 15, resolved with NPM 22 - 162 were randomised to treatment: 81 lansoprazole, 81 placebo - 66 premature discontinue double-blinded treatment: 32 lansoprazole; 34 placebo - 96 completed double-blinded treatment: 49 lansoprazole; 47 placebo **Characteristics** Characteristics (range): Lansoprazole n = 81; Placebo n = 81 - Age, median weeks: 16 (4 to 49); 18 (4 to 51) - Gestational age at birth, weeks: 35 (25 to 39); 35 (26 to 38) - Premature: 20; 24 - Sex, % male: 47; 53 - Median weight, kg: 5.9 (4 to 9); 6.2 (4 to 11) - Median length, cm: 61 (53 to 78); 62 (52 to 80) - I-GERQ-MH score: 13 (7 to 21); 13 (3 to 23) **Inclusion criteria** - Aged 28 days to <12 months (corrected age of 44 weeks but <12 months) for preterm infants - Symptomatic GERD (crying,	**Interventions** Non-pharmacological management: - Parents reqired to institute and record in a daily diary on NPM stratergies as part of inclusion/exclusion criteria - Reducing tobacco smoke exposure; feeding strategy (burping, thickened, dairy avoidance, size and frequency); positional management (minimising seated, awake supine, avoid vigorous handling) Treatment period: - Lansoprazole (Takeda) formulated as an investigational suspension of microgranules for weight-based oral dosing, was administered once daily, preceded and followed by a ≥30 minute fast, at 0.2 to 0.3 mg/kg/day for infants aged ≤10 weeks and at 1.0 to 1.5 mg/kg/day for those aged >10 weeks for 4 weeks - Placebo fomulated identically but without active drug by the same manufacturer, was dosed comparably - Nonpharmacological management judged to be benficial was continued at	**Details** Ethics - Informed consent obtained from parents/guardians - Study protocol approved for US sites by central or local Insitutional Review Boards, Polish by a Central Ethics Committee and Polish Ministry of Health Setting 16 centers: 8 in USA and 8 in Poland Randomisation and concealment - Randomised blindly at a drug:placebo ratio of 1:1 - Assignment via web-based system according to computer generated system - Double blind treatment concealment to parents and study personnel - Blinding broken for emergency situations Method of monitoring - Questionnaire (I-GERQ-MH) completed by parents adapted from the Infant Gastroesophageal Reflux Questionnaire identifies symptoms, provocative factors and other possible causes of symtpoms (computed into a score) - Responder status was determined at week 4 (using double-blind week for	**Results** Outcome: Lansoprazole n=81; Placebo n=81 - Primary efficacy: Responder rate, n: 44 (54%); 44 (54%) - Discontinued due to nonefficacy: 28 (35%); 29(36%) % of feeds/week - Cry: -20; -20 - Regurgitate: -14; -11 % of days/week: - Feed refusal: -14; -10 - Arching: -20; -18 - Coughing: 0; -9 - Wheezing: -5; -6 Hoarseness: +2; -5 Global assessment of improvement at 4 weeks: Parent: 45 (56%); 41 (51%) Physician: 44 (55%); 40 (49%) Adverse effects: - Total: 50 (62%); (46%); p = 0.058 - Upper respiratory infections 18; 17 - Constipation 9; 3 - Dermatitis, eczema 8; 6 - Ear infections 8; 5 - Fever 8; 2 - Lower respiratory tract infection 6; 2 - Respiratory tract infection: 6; 2 - Rhinorrhea 6; 4 - Candidiasis 5; 3 - Diarrhea 4; 5	**Limitations** - No account taken of between center effects on outcomes - No assessment of effect of other treatments **Other information** - Lansoprazole open-label (n=55) efficacy and adverse events also reported - I-GERQ-MH questionnaire described in appendix 1 - Details on medication, dispensing, randomisation, blinding and complicance tracking given in appendix 1

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
persisted despite a >1 week course on non-pharmacolgic management. **Study dates** June 29, 2006 to May 16, 2007 **Source of funding** Takeda Global R&D sponsored the clinical trial and data analysis	fussing, irratibility) during or within 1 hour after feeding for at least 1 week despite non-pharamacological managment Informed consent - Weight > 2.0 kg - Daily diary documented crying during or within 1 hour after ≥25% of feeds during the 4 days before randomisation despite ≥7 days of specified NPM stratergies **Exclusion criteria** - Previous use of PPIs within 30 days - Histomine-2 receptor antagonist within 7 days (others given in appendix 1)	the investigator's discretion and documented - Concomitant treatment was allowed as needed but were retained at the same dosage if possible and recorded After ≥1 week of double-blind treatment, infants discontinuing the treatment due to inefficacy as judged by the site investigator were eligible for open-label lansoprazole at the investigator's discretion. Open-label inital visit functioned as the doubl-blind termination visit.	subjects discontinuing early) and was defined as a ≥50% reduction from baseline in either percentage of feedings with crying episodes or duration (minutes) of episodes averaged across feedings - Responder rate was the percentage of subjects who were responders at week 4 <u>Outcome measures</u> - Primary efficacy variables were daily diary-documented number and duration of crying episodes during or ≤1 hour after feeding (≥50% reduction in measures of feed related crying) - Secondary: Regurgitation, arching back, feed refusal, coughing, wheezing, hoarseness; global assessment of outcome by parent and by physician; compliance with treatment and data collection. <u>Statistical analysis:</u> - Sample size of 160 provided ≥80% power to establish the superiority of lansoprazole treatment when the overall study dropout rate was ≤20% - Differences between groups compared using z-test or Fisher's exact test - Intention-to-treat analysis	- Vomitting 4; 1 - Alkaline phosphatase increase 2; 5 - Viral infection 2; 5 <u>Serious adverse events</u> - Including: infection, diarrhoea, dehydration, illeus, cellulitis - All serious adverse events were hospitalised - 10 (12%); 2 (2%); p = 0.032 All outcomes were non-significant at p = 0.05	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Follow-up: - Telephone calls and a safety folow-up visit with global symptom assessment of symptoms 30 days after the last dose of any study drug (double-blind or open-label) - Daily diaries 7 days before follow-up visit		
Full citation Tolia,V., Calhoun,J., Kuhns,L., Kauffman,R.E., Randomized, prospective double-blind trial of metoclopramide and placebo for gastroesophageal reflux in infants, Journal of Pediatrics, 115, 141-145, 1989 **Ref Id** 219915 **Country/ies where the study was carried out** USA **Study type** Randomised, prospective, double-blind, cross-over controlled trial	**Sample size** 30 **Characteristics** - Age range 1 to 9 months - Median age 2 months - 17 boys and 13 girls - No underlying disorders (prematurity or chronic pulmonary, renal, neurologic or hepatic disorders) - Average daily occurrence of all symptoms, before treatment, mean (SD): 13.0 (3.0) pretreatment value significantly different from placebo or metoclopramide values p<0.005 **Inclusion criteria** - pH probe confirmed GER - Only if the EPM result was abnormal during the initial 8 hours	**Interventions** - Received either metoclopramide or placebo for the first week and switched to the alternate treatment during the second week of the study - Metoclopramide: 0.1 mg/kg x4 per day 30 minutes before feeding for 1 week - Placebo: identical vehicle to metoclopramide and prescribed in a volume equal to 0.1mg/kg/dose of active metoclopramide - Parents instructed to use the same volume of formula per feeding during the 2 weeks of the study as during the pretreatment period - Positioning or thickening of feeding, were kep constant during the pretreatment and both feeding periods	**Details** Ethics - Parental informed consent - Study protocol approved by Children's Hospital of Michigan Institutional Review Board Setting Not stated Randomisation and concealment - Neither the physician nor the parent knew which medication was given during each period - The dispensing pharmacist had access to the randomisation code Method of evaluation - Parent reported daily diary of symptoms (number of episodes of spitting up, cough, choking, stridor, apnea and nasal regurgitation) - Eight hour EPM was	**Results** Outcome: metoclopramide; placebo Mean (SD) Symptoms and weight change - Average daily occurrence of all symptoms: 5.6 (1.20); 6.5 (1.3) - Average daily weight change (gm) during treatment periods: 36.8 (6.1); 35.2 (11.6) - When the patients were statified by age, infants >3 months of age had significantly increased weight gain during metoclopramide treatment, mean (SEM): 34(8); 1(11); p=0.05 Esophageal pH probe N=30 - % of time pH ≤4.0, reflux index: 10.3 (95% CI 2.4 to 22.8); 13.4 (95% CI 2.8 to 30.5); p<0.001 - Total number of episodes of pH <4.0: 25.0 (3.4); 22.4 (2.5) - Number of episodes > 5 minutes: 2.6 (0.5); 2.0 (0.3)	**Limitations** - No washout period between cross-over - Method of randomisation and allocation not explained in detail **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study Investigate efficacy of orally adminstered metoclopramide in the treatment of GER in infants less than 1 year of age **Study dates** Not stated **Source of funding** - Supported by Children's Hospital of Michigan Research Endowment Funds - A.H. Robins Company supplied metoclopramide and placebo	**Exclusion criteria** - Underlying disorders (prematurity or chronic pulmonary, renal, neurologic or hepatic disorders) - Received metoclopramide before study entry		repeated after the fourth day of each treatment period, significant reflux if pH <4.0 for more than 5% of the total monitoring period - Gastroesophageal scintigraphy after the fourth day of each treatment period, gastric emptying was considered abnormal if >70% of radioactivty of the ingested formula, corrected for decay, remained at the end of 1 hour - EPM results were interpreted as indicating significant reflux if pH <4 for >5% of total monitoring period - Presence of radioactivity in the esophagus during 1 hour of scintigraphy indicative of GER - Weight gain <u>Outcome measures</u> - Reflux index - Number of reflux episodes < 4 - Number of episodes > 5 minutes - Daily report of all symptoms <u>Statistical analysis</u> - Paired t-test - Data for reflux index was log transformed to allow analysis using t-test	<u>Scintigraphic observations</u> - Gastric emptying in 60 minutes (%): 35.1 (95% CI 22.6 to 48.8); 31.5 (11.1 to 56.6) - Fraction of patients with GER: 24 of 27; 24 of 27 No side effects observed during either study period	
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Cresi,F., Marinaccio,C., Russo,M.C., Miniero,R., Silvestro,L., Short-term effect of domperidone on gastroesophageal reflux in newborns assessed by combined intraluminal impedance and pH monitoring, Journal of Perinatology, 28, 766-770, 2008 **Ref Id** 219990 **Country/ies where the study was carried out** Italy **Study type** Randomised controlled trial **Aim of the study** Evaluate the short-term effects of domperidone on GER in symptomatic newborns by means of the simultaneous measurement of impedance and oesophageal pH. **Study dates** Not stated	26 studied: 13 control, 13 treatment **Characteristics** 26 neonates: 14 boys, 12 girls Characteristic: control; treatment; p value Mean (SD) - Age, days: 29.5 (7.4); 24.7 (13.7) - Gestational age, weeks: 37.2 (3.3); 38.1 (2.2); 0.22 - Postconeptional age, weeks: 42.8 (4.8); 41.6 (2.1); 0.20 - Weight at enrollment, g: 380.0 (850.6); 3825.8 (353.7); 0.10 - Length, cm: 52.5 (3.9); 50.0 (3.3); 0.15 **Inclusion criteria** - Admitted to neonatal unit, with clinically suspected of having GORD (feeding problems, vomiting, irratibility, ALTE and failure to thrive) - Not responded to conservative therapy **Exclusion criteria** - Treatment with drug known to act on the GI tract or interefere with action of domperidone (antacids, anti-H2 agents, proton pump inhibitors, sympathicolytics, anticollinergics, opioid analgesics	- Treatement group: Domperidone 0.3 mg/kg per os with their 8 hour and 16 hour meals. - Control treatment not described - All infants received 25 ml/kg per meal maternal or formula milk from a feeding bottle every 4 hours - Kept supine on a surface inclined at 30 degrees	Ethics - Research protocol approved by local ethics committee - Written consent obtaine from parents Setting Neonatal pathology centre of the Regina Margherita Children's Hospital, Turin Randomisation Treatment was randomly allocated by odds on pair from random-number table Method of monitoring - MII/pH tracings examined by a single operator - Three consecutive 8 hour observation periods were identified for each MII/pH tracing to create one baseline period (P0) from the first to the eighth hour and two treatment periods (P1, P2) from the eighth to the sixteent and the sixteenth to the twentieth hour - A GER episode was defined as a decrease of impedance over two channels and folowed by an increase in impedance to baseline values - The duration of an episode was defined as the time, in seconds, between its onset at the 50% drop in	- Reflux frequency: less reflux in control group $p < 0.05$ at 8 and 16 hours (P1 and P2) - Duration of reflux: less in treatment group $p < 0.05$ at 8 hour only (P1) - The treatment group displayed significant increase in reflux frequency during periods P1 and P2 compared with P0 (4.06±1.16 vs 2.8±1.42; p=0.001), and a decrease in duration (16.68±4.49 vs 20.18±7.83; p=0.043), whereas there were no differences in the maximum proximal levels reached by the refluxes (3.37±0.45 vs 3.34±0.94; p=0.894) and their pH (4.72±0.69 vs 4.60±1.17; p=0.634) - No ECG and oximetric alterations, nor other side effects were noted	- Control treatment not described - Method of concealment of allocation not described - Results displayed in figures, few outcomes are reported separately, not presented in format that could be used in meta-analysis **Other information** MII/pH was interrupted in one patient of the treatment group prior to the end of the study, this subject and the corresponding control were discarded when comparisons were made with the P2 period

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding - Not stated - Declare no conflict of interest	and CYP3A inhibitors) - Infection, metabolic or CNS disease		impedance from baseline relative to nadir and bolus exit at the 50% recovery point from nadir to baseline recorded at channel 1 <u>Outcome measures reported</u> - Reflux frequency per hour - Reflux duration in seconds - Reflux pH (mean of the minimum pH value during each reflux) - Reflux level expressed as the number of channels - Reflux proximal extent <u>Statistical analysis</u> - Each treated patient was matched with the nearest control considering postconceptional age at the day of enrollment - Paired t-test		
Full citation Bellissant,E., Duhamel,J.F., Guillot,M., Pariente-Khayat,A., Olive,G., Pons,G., The triangular test to assess the efficacy of metoclopramide in gastroesophageal reflux, Clinical Pharmacology and Therapeutics, 61, 377-384, 1997 **Ref Id**	**Sample size** - 44 enrolled: 21 placebo, 23 metoclopramide - Caen centre included 30 patients - Lisieux centre included 14 patients - 39 infants evaluated on day 14: 20 placebo, 19 metoclopramide **Characteristics** <u>Characteristics: placebo; metoclopramide; p value</u> - Number: 20; 19	**Interventions** - Metoclopramide (Synthelabo, Paris) 2.6 mg/ml (0.1 mg/drop). 2 drops/kg x3 per day before a meal for 14 days - Placebo: not stated - Positional management was applied - Vitamin D, antibiotics and paracetamol permitted - Exclusion drugs were not permitted during the study period	**Details** <u>Ethics</u> - Study protocol approved by Ethics Comittee of Cochin-Port-Royal School of Medicine - Informed written consent obtained from parents <u>Setting</u> Two centres: Caen and Lisieux, France <u>Method of randomisation and concealment</u> - Randomised, double-blind.	**Results** Outcome, mean (SD): placebo; metoclopramide Number of infants: 20; 19 <u>Esophageal pH</u> - Time at pH <4, hours: 1.4 (1.9); 1.2 (1.6), p=0.68 - % time at pH < 4.0: 8.1 (11.7); 6.7 (9.2), p = 0.68 - Reflux > 5 minutes: 3.0 (3.5); 1.9 (3.0), p = 0.33 - Reflux at pH < 4: 43 (26); 63 (136), p = 0.53 - Mean reflux, minutes: 1.8 (1.3); 1.9 (2.1), p=0.96	**Limitations** - Method of blinding, randomisation and concealment not described - Number of patients who did not meet inclusion criteria not reported - Care may differ across the two centres <u>Attrition bias:</u> - 5 withdrawn from statistical analysis: 1 placebo, 4

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
237188 **Country/ies where the study was carried out** France **Study type** Randomised, double-blind, placebo controlled trial **Aim of the study** Assess the efficacy of a repeated dosing regimen dervived from these findings. **Study dates** July 20, 1990 to March 10, 1994 **Source of funding** Laboratoires synthelabo (commercial pharmaceutical company)	- Age, days: 122±79; 87±67; 0.15 - Sex male: 15 (38.5%); 12 (30.8%); 0.42 - Weight, kg: 5.8±1.8; 5.3±2.0; 0.40 - Height, cm: 60±8; 57±7; 0.17 - Regurgitations: 12; 10; 0.64 - Vomiting: 12; 11; 0.89 - Cry or agitation: 6; 3; 0.50 - Paleness or cyanosis: 7; 3; 0.31 - ENT disease: 6; 3; 0.50 - Previous treatment: 3; 2; 1.00 - Present treatment: 3; 4; 0.94 **Inclusion criteria** - 44 weeks postconceptional age to 8 months of postnatal age - GERD diagnosed on a 24-hour esophageal pH recording when the % of time pH <4 was ≥5% of recording duration **Exclusion criteria** - Concomitant disease: gastrointestinal (esophagitis, esophageal stenosis, diaphragmatic hypoplasia or hernia, gastroduodenal ulcer, chronic disease, or antireflux surgery), acute infection, repeated bronchitis, hemorrhagic syndrome, systemic illness, dehydration, disease of the nervous system, hypoprotidemia, renal failure, porphyia or diabetes - Received treatment within 1 week of study starting		Not described - Esophageal pH recordings analysed by a treatment-blinded investigator Method of monitoring 24 hour pH monitoring at baseline and at 14 days Outcome measures: - Relative variation between day 0 and 14 of the precentage of time pH <4 - Number of reflux episodes >5 minutes - Number of reflux episodes at pH <4 - Duration of a mean reflux and duration of the longest reflux - Weight - Four class qualitative evaluation of the treatment efficacy obtained from parents Statistcial analysis: - Anticipated a 20% reduction in % of time at pH <4 between day 0 and 14, the mean improvement with metoclopramide was to detect 0.70 (50% benefit as compared with placebo), SD=0.50, type 1 and type 11 error rate rate =0.05, required a sample size of 46 - Planned, monitored, and analysed with the triangular test to stop it as early as possible	- Longest reflux, minutes: 15 (17); 18 (30), p = 0.71 Weight, kg (day 14): 5.9 (1.7); 5.6 (1.9), p=0.61 Adverse events: - One placebo patient stopped treatment on day 5 because of vomitting - In the metoclopramide group, the treatment was stopped in one infant for repeated apneas on day 8, in a second infant for vomitting on day 2, and in a thirs infant for irritability, agitation, and bottle refusal on day 2 An aggravatoin or a lack of change on the one hand and an improvement or complete recovery on the other hand were noticed in 5 and 15 patients with placebo and in 9 and 10 patients with metoclopramide, chi-squared=2.12, p=0.15	metoclopramide - 2 metoclopramide patients lost to follow-up, and 1 placebo and 2 metoclopramide discontinued treatment before day 14 (on days 5, 2 and 2 respectively) for apparent inefficacy **Other information** - Esophageal pH recording data also reported at time of inclusion, day 0 (table 2) - Date of sequential analysis and cumulated numbers of evaluated infants at each analysis also reported (table 3)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(metoclopramide, domperidone, trimebbutine, cisapride, alizapride, cholinegic druge, metopimazine, spasmolytic agents, atropine, antacid, H1 antihistamines, aspirin or NSAIDs) - Steriods or hepatic enzyme inducers or inhibators within 1 month		- Student t-test for quantitative - Pearson chi-squared or Fisher exact test to compare qualitative		
Full citation Simeone,D., Caria,M.C., Miele,E., Staiano,A., Treatment of childhood peptic esophagitis: a double-blind placebo-controlled trial of nizatidine, Journal of Pediatric Gastroenterology and Nutrition, 25, 51-55, 1997 **Ref Id** 220132 **Country/ies where the study was carried out** Italy **Study type** Randomised, double-blind, placebo-controlled trial	**Sample size** - 26 recuited: 13 nizatidine, 13 placebo - 24 completed trial, one placebo patient was withdrawn because of worsening symptoms and one nizatidine was withdrawn because of urticariod rash - 19 had pH monitoring results **Characteristics** <u>Characteristic: Nizatidine; Placebo</u> - Number of patients: 13, 13 - Sex male/female: 9/4, 8/5 - Median age, years (range): 2.08 (0.5 to 12); 1.16 (0.5 to 9.5) - Abdominal pain and colic (in infants) (%): 91.7; 83.3 - Retrosternal pain (%): 33.3; 41.6 - Regurgitiaion (%): 58; 58 - Vomitting (%): 91.7; 83.3 - Growth failure (%): 15.3; 23.0 - Respiratory symptoms (%): 23.0; 7.6	**Interventions** - Nizatidine 10mg/kg b.i.d for 8 weeks or a matching placebo - The pharmalogical presentation of nizatidine and placebo was a 150mg capsule - Oral dose was given by mixing the content of a 150mg nizatidine capsule with 10ml water, resulting in a final concentration of 15mg/ml of niztadine or placebo - In all patients, positional therapy and dietry manipulation with thickened feeds (dry rice cereal) were recommended	**Details** <u>Ethics</u> - Investigation approved by the local institutional review board - Informed written consent obtained from parents <u>Setting</u> Not stated <u>Randomisation and concealment</u> Randomised, double-blind. No further details provided. <u>Method monitoring</u> - 24-hour intraesophageal pH monitoring - Enscope evaluation of the oesophagus with biopsy - Esophagitis graded according to Cucchiara et al - During endoscopy, macroscopic changes of esophageal mucosa were evaluated accoridng to a scale - Daily diary card maintained by parents to record	**Results** Outcome: Nizatidine; Placebo <u>pH variables, median (range)</u> - N=10; N=9 - Percentage of reflux episodes: Before 13.8 (8.7 to 23.7); 12.4 (4.47 to 28) After 4.3 (1.5 to 11.2); 10.4 (4.1 to 18.8) - Number of reflux episodes: Before 210 (70 to 375); 148.3 (51 to 238) After 85.8 (42 to 227); 123 (32 to 360) - Number of reflux episodes >5 minutes: Before 6.2 (1 to 11); 5.7 (1 to 16) After 1.7 (0 to 6); 5.4 (2 to 10) - Duration of longest episode, minutes: Before 22.9 (10 to 43); 26.7 (3 to 80) After 11.8 (4 to 40); 25.1 (3 to 73) <u>Clinical scores, mean (SD), N=24</u> - Abdominal pain colic:	**Limitations** - Randomisation and blinding unclear - Small sample size - Only 19 out of 24 children underwent pH-metry evaluation - Subjective scoring systems - Unclear inclusion criteria **Other information** - Grading of symptoms of reflux esophagitis described in table 1 - Histology and endoscopy before and after treatment in infants and in children >1 year also reported (table 3)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study Evaluate the therapeutic efficacy and tolerability of nizatidine inchildren affected by reflux oesophagitis **Study dates** Ocober 1993 to June 1994 **Source of funding** Not stated	**Inclusion criteria** Patients with reflux oesophagitis **Exclusion criteria** - Treatment with ulcerogenic or anti-reflux agent - Systemic extra-intestinal diseases - Neurological disorders - History of previous surgery		frequency and severity of GER symptoms - GER episode defined as a decrease in the distal esophageal pH <4 for ≥20 seconds, and pH metry was considered pathological when total acid esophageal exposure time was >4% - Physical and symptomatologic assessment was performed after 4 weekf of therapy - After 8 weeks of treatment, 48 hours before the end of therapy, clincal evaluation, laboratory tests, pH probe study, and endoscopy with biopsy were performed <u>Outcome measures</u> - Oesophagitis based on biopsy histology - Muscosal changes on endoscope - pH results: % time pH <4, number of reflux episodes, number of episodes > 5 minutes, duration of longest episode, percentage of reflux episodes - Parent daily diary of symptoms: abdominal pain, chest pain, regurgitation and vomiting based on score of 0 to 3 - Adverse events <u>Statistcial analysis</u> Wilcoxon's rank sum or Fisher's exact test	4 weeks 1.4 (1.1); 2.2 (1.0) 8 weeks 0.7 (1.2); 1.6 (1.1) - Chest pain, pyrosis: 4 weeks 1.7 (1.1); 1.8 (0.8) 8 weeks 1.0 (1.7); 1.6 (0.9) - Regurgitation: 4 weeks 1.3 (1.1); 2.2 (1.3) 8 weeks 0.3 (0.7); 1.7 (1.4) - Vomiting: 4 weeks 0.8 (0.9); 2.1 (1.1) 8 weeks 0.4 (0.7); 1.6 (1.7) - Reduction in symptoms (>80%) after 8 weeks of therapy in comparison with the baseline period was found in eight patients on nizatidine (66.6%) and in three on placebo (25%) <u>Endoscopic results</u> - Nine of 12 patients treated with nizatidine (75%) were cured, as opposed to only two of the patients treated with placebo (16.7%) - In the nizatidine group, two patients (16.7%) showed histological findings improved for three (25%) patients, remianed unchanged in six (50%) and worsened in one (8.3%). - Seven of the 11 histologically cured patients (63.6%) had a normal endoscopic picture - In three of four patients in the placebo group (75%) with esophageal pretreatment lesions, the pretreatment histological picture was unchanged	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				No adverse events were reported	
Full citation Leung,A.K.C., Lai,P.C.W., Use of metoclopramide for the treatment of gastroesophageal reflux in infants and children, CURR THER RES, CLIN EXP, 36, 911-915, 1984 **Ref Id** 237226 **Country/ies where the study was carried out** Canada **Study type** Randomised controlled trial **Aim of the study** Report experience with metoclopramide in the treatment of gastroesophageal reflux in pediatric patients. **Study dates**	**Sample size** 41: 32 with metoclopramide and 9 controls **Characteristics** - 19 males, 22 females - Mean age at diagnosis was 160 days (range 21 to 1215) - 38 born at term, three patients born between 34 and 36 weeks of gestation - 7 patients had one of the following anomalies: Ebstein's anomaly, Ebstein's anomaly with Wolf-Parkinson-White phenomenon, pulmonary valve stenosis, diaphragmatic hernia and Ladd's syndrome, inguinal hernia and Bell's palsy - Mean weight at diagnosis 6.35kg (range 2.73 to 17.2) Clinical presentation: - 35 with persistent regurgitation - 4 with regurgitation and faliure to thrive - 1 with regurgitation and apnea - 1 with regurgitation, apenoa and faliure to thrive **Inclusion criteria** Radiological evidence of	**Interventions** - Metoclopramide (Maxeran) at 0.5 mg/kg/day divided in 4 doses given orally 10 to 20 minutes before feedings - Control not stated - Parents were instructed to place the infants in a 30 degree elevated prone position whenever applicable - Patients were followed at monthly intervals and treated until their symtoms had subsided	**Details** Ethics Informed consent obtained Setting Not stated Method of randomisation and blinding Not stated Method of monitoring Parent reported the frequency of regurgitations Outcome Frequency of regurgitation Statistical analysis Student t-test	**Results** - Compared to the control group, the frequency of regurgitation in the treated group decreased to 3.8 episodes per day (SD 3.9, t=2.0, p<0.05) at week 1, 2.9 episodes per day (SD 3.6, t=2.7, p<0.01) at 2 weeks and 1.6 episodes per day (SD 2.0, t=4.6, p<0.005) at 4 weeks following therapy - Five patients had failure to thrive with weight less than the third percentile prior to metoclopramide therapy, after one month they experienced a mean weight gain of 9.8% (range 4.3 to 17.6) Duration of metoclopramide treatment until total subsidence of regurgitation 0-1 month: 9 1-2 months: 9 2-3 months: 9 3-4 months: 4 >4 months: 1 Adverse effects: - Two patients had apnea associated with gastroesophageal reflux, apneic spells resolved within 10 days of treatment - Two patients had slight drowsiness	**Limitations** - Method of randomisation and concealment not described - Control group treatment not explained (untreated controls) - Reason for unbalanced groups not explained - Results presented in figures - Adverse effects not reported for each treatment group **Other information** - Two patients had aspiration of barium into the trachea and another patient had an apneic spell during the radiological examination - One patient developed an acute oculogyric crises 36 hours after he was mistakenly given four times the prescrobed dose, taken to the emergency room

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
August 1982 to December 1983 **Source of funding** Not stated	gastroesophageal reflux to the level of the oropharynx **Exclusion criteria** Not stated			- Two patients had irritability and fussiness	- Figure 1 displays regurgitation episodes at the time of diagnosis, and 1, 2 and 4 weeks after treatment
Full citation Davidson,G, Wenzl,TG, Thomson,M, Omari,T, Barker,P, Lundborg,P, Illueca,M, Efficacy and Safety of Once-Daily Esomeprazole for the Treatment of Gastroesophageal Reflux Disease in Neonatal Patients, Journal of Pediatrics, 163, 692-698.e2, 2013 **Ref Id** 282181 **Country/ies where the study was carried out** 3 centres: Australia, Germany and the UK **Study type** Randomised, double-blind, placebo-controlled, multicentre study **Aim of the study**	**Sample size** - 52 enrolled: 24 randomised by the Australian site, 17 by the German site and 11 by the UK site - 26 esomeprazole group, 26 placebo group - The study was discontinued prematurely because of poor enrollment - One patient in the esomeprazole group was excluded from the modified ITT analysis because of invalid efficacy measurements, but was included in the safety analysis - One patient in the placebo group completed the study, but was lost to follow-up between study completion and the safety follow-up visit **Characteristics** <u>Characteristics (mITT population): esomeprazole n=25; placebo n=26</u> - Mean postnatal age, days (SD): 48.1 (29.8); 46.5 (31.2) - Median (range): 43.0 (7 to 104): 38.0 (9 to 111) - Mean gestational age, weeks	**Interventions** - Esomeprazole 0.5mg/kg or placebo once daily for up to 14 days - Study drug or placebo concentrate were thawed at room temperature and diluted with a thawed sodium bicarbonate solution prior to use - Each dose was administered in a volume of 2ml/kg of liquid (0.5mmol sodium bicarbonate and 0.5mg esomeprazole/placebo of diluted solution per kg) - Administered via oral gavage or nippling 30 minutes before morning feeding and followed by administration of 5-10ml of sterile water or formula	**Details** <u>Consent:</u> - Written informed consent was obtained from each neonate's parent/guardian before any study procedure was performed - Ethical principals of the Declaration of Helsinki <u>Setting:</u> Inpatient, 3 centres (Australia, Germany, UK) <u>Randomisation and concealment:</u> - Block randomisation, stratified by centre - Randomisation of patients was strictly sequential <u>Outcome measures:</u> - Simultaneous esophageal pH, impedance monitoring, cardiorespiratory monitoring, and 8-hour video monitoring were performed at baseline and on final study day (end of 14 day treatment or early discontinuation) - Two blinded central readers independently reviewed 8 hours of	**Results** <u>Normalised number of GERD-related signs and symptoms from video recording and cardiorespiratory monitoring: esomeprazole n=25; placebo n=26</u> Change from baseline, mean (SD) <u>Gastrointestinal</u> - Vomitting: -0.58(4.68); 0.70(6.46); p=0.4227 <u>Neurobehavioural</u> - All neurobehavioural: -6.20(22.44); -1.86(27.66); p=0.9380 - Gagging: -2.76(8.95); -1.84(4.46) - Back arching: -3.39(16.07); 0.60(14.31) - Irritability/crying/fussing: -0.05(17.27); -0.61(22.85) <u>Cardio-respiratory</u> - All cardo-respiratory: -21.22(71.85); -23.63(38.88); p=0.8887 - Bradycardia: 0.81(7.13); -0.62(3.26) - Oxygen desaturation: -21.62(71.23); -21.14(36.39)	**Limitations** - Number of patients who did not meet inclusion criteria not reported - Care may differ across the 3 centres - Blinding unclear - Placebo unclear **Other information** - Baseline and end of treatment values also reported for the normalised number of GERD-related signs and symptoms from video recording and cardiorespiratory monitoring in table 2 - Modified ITT included all randomised patients who received ≥1 dose of study medication and had valid efficacy measurements at both baseline and final visit - Patients were included in the safety analysis if they received ≥1 dose of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To evaluate the efficacy and safety of proton pump inhibitors in infants aged <1 year with GERD **Study dates** November 30, 2006 to April 14, 2009 **Source of funding** Sponsored by AstraZeneca LP. AstraZeneca was involved in the design and conduct of the study; collection, analysis, and interpretation of the data; and the preparation, review, and approval of this manuscript.	(SD): 31.4 (4.9); 31.7 (4.9) - Median (range): 31.0 (24 to 40); 30.5 (24 to 39) - Boys n(%): 10 (40.0); 11 (42.3) - Girls n(%): 15 (60.0); 15 (57.7) - Mean height, cm (SD): 46.6 (4.4); 47.3 (5.3) - Median (range): 46.0 (40.0 to 56.0); 45.5 (40.0 to 57.5) - Mean weight, kg (SD): 2.70 (0.8); 2.9 (1.2) - Median (range): 2.5 (1.6 to 4.7); 2.5 (1.7 to 6.2) **Inclusion criteria** - Infants who were full-term or had a gestational or post-conception age of 28 to 44 weeks - Inpatients in a Neonatal Intensive Care Unit special care nursery or equivalent hosptal ward at study entry, and expected to remain inpatients for the duration of the treatment period - <28 weeks gestation considered if they met inclusion criteria and could undergo all study-related procedures - Suspected of having any two of the following (reproducible during an 8 hour video monitoring period): apnea with or without bradycardia and with or without oxygen desaturations, vomitting or gagging, and irritability or pain at least eery second feed or at leaast twice every 8 hours		integrated data to identify that start and stop times of predefined sign and symptoms of GERD and types of reflux events - The primary efficacy outcome was change from baseline to end of treatment in the total number of GERD symptoms (video recording) and GERD-related signs (cardiorespiratory monitoring) <u>Statistical methods:</u> - Modified intention-to-treat analysis - Minimum of 90 patients to achieve 38 evaluable patients in each study arm, power≥80%, two-sided α=0.05 to detect a difference between esomeprazole and placebo in the change in symptomatic episodes from baseline - ANCOVA assessed the change from baseline in the total number of symptoms and GERD-related signs and cardiorespiratory monitoring - Number of events at baseline and finial visit transformed via a log (1+x) - Differences between groups having symptoms/signs of GERD compared using Fisher exact test	- Apnea: -0.41(1.73); -1.87(5.66) - The mean change from baseline in the total number of reflux episodes (LSM) based on 24 hour pH/impedance monitoring was not significantly different between the two treatment groups (esomeprazole -7.43, placebo -0.2, p=0.5338) - Decreases in the number (LSM) of acidic reflux episodes and increases in the number of weakly acidic episodes were significantly greater with the esomeprazole group compared with the placebo group (-30.4 vs -4.32 [p<0.0001] and 25.05 vs 0.46 [p=0.0207], respectively) - The mean change from baseline in the percentage of time that pH was <4.0 significantly decreased in esomeprazole-treated patients compared with placebo-treated patients (-10.7 vs 2.2, p=0.0017) - The mean percentage of time tat pH was 4.0 to 6.9 in the esomeprazole group significantly increased from baseline compared with placebo (9.8 vs -2.6, p=0.0022) <u>Adverse events:</u> - Six (23.1%) patients in the esomeprazole group experienced a total of 10 AEs and nine (34.6%) patients in the	study medication and had ≥1 value at post-baseline assessment - For inclusion in the pharmacodynamic analyses patients required ≥18 hours of pH data with pH 0 to 8 range at baseline and final visit and no continuous hour with data outside the pH 0 to 8 range

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	Exclusion criteria - History or current need for resectional or reconstructive surgery of the gastrointestinal tract or could require surgery during the study - Active gastrointestinal bleed, allergic gastroenterpathies, eosinophilic gastroenteritis, bleeding disorders, active seizure disorder, ongoing treatment for seizure disorder, acute pancreastitis, meningitis, or acute respiratory distress - Concomitant medications (eg antimetics, H2-receptor antagonists, narcotics, warfarin, bismuth-containing products, barbiturates, anti-convultants, antineoplastic agents, sucralfate, or promotility drugs)			placebo group experienced a total of 14 AEs - Most commonly reported AEs by organ system class: gastrointestinal disorders 9.5%, infections/infestations 7.7%, investigations 5.8% - Most commonly reported AE was decrease in oxygen saturation (esomeprazole 2, placebo 1) - No severe adverse events were reported in the esomeprazole group, four (neonatal bradycardia, cyanosis, inappropriate device signal detection, and infantile apneic attack) were reported in three placebo group patients (11.5%) - One patient in the placebo group experienced an AE considered to be treatment-related (neonatal anemia)	
Full citation Davidson,G., Wenzl,T.G., Thomson,M., Omari,T., Barker,P., Lundborg,P., Illueca,M., Efficacy and safety of once-daily esomeprazole for the treatment of gastroesophageal reflux disease in neonatal patients, Journal of Pediatrics, 163, 692-698, 2013	**Sample size** 26 esomeprazole 26 placebo **Characteristics** **<u>Characteristic: esomprazole; placebo</u>** Number: 25 (26 randomised, 1 excluded from analysis); 26 Mean postnatal age (SD), days: 48.1 (29.8); 46.5 (31.2) Mean gestational age (SD), weeks: 31.0 (4.9); 31.7 (4.9) Mean BMI (SD), kg/m2: 12.2	**Interventions** Esomeprazole (0.5 mg/kg) daily for 14 days Placebo daily for 14 days Each dose administered in a volume of 2 mL/kg of liquid. No description of other treatments being allowed or prevented.	**Details** **<u>Ethics approval</u>** Ethical approval not described **<u>Sample size</u>** Planned randomisation of 90 patients to achieve 38 evaluable patients in each arm for >80% power and alpha of 0.05 to detect difference between groups in symptomatic episodes. **<u>Randomisation</u>** Sequential randomisation	**Results** Normalised numbers for change and end of study. No statistcial differences identified. **<u>Outcome, mean (SD): esomerprazole; placebo</u>** All events: change -28.01 (77.70); -24.79 (44.25): end 156.65 (75.11); 158.31 (75.89) Vomiting: change -0.58 (4.68); 0.70 (6.46): end 5.21 (6.75); 4.87 (5.93) Gagging: change -2.76 (8.95); -1.84 (4.46): end 5.13 (5.52); 4.17 (4.80) Back arching: change -3.39	**Limitations** - Small sample size - Method of blinding not described in detail - Large number of comparisons undertaken **Other information** - Study stopped early due to poor recruitment - Highly selected population - inpatient

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 306312 **Country/ies where the study was carried out** Australia, UK & Germany **Study type** Multi-centre double-blind, placebo-controlled phase III trial **Aim of the study** Assess the difference between Esomeprazole and placebo in the treatment of signs and symptoms of GERD as oberved by 8-hour video and cardiovascular monitoring in neonatal patients. **Study dates** November 2006 and April 2009 **Source of funding** AstraZeneca	(1.5); 12.6 (2.6) **Inclusion criteria** Full-term or 28 to 44 weeks (<28 if they were believed to be suitable) Inpatients on NICU or equivalent and likely to remain so for duration of study Two or more of following symptoms: apneoa with or without bradycardia and with or without oxygen desaturation, vomiting or gagging, and irritability or pain at least every second feed or at least twice every 8 hours. And reproduced on video monitoring. **Exclusion criteria** History or need for resectional or reconstructive surgery Disease or condition (active gastrointestinal bleed, etc.) Concomitant medication required (H2RAs, promotility drugs, etc.)		based on block s and stratified by center **Blinding** Double blind, but not specified who was blinded. **Statistcial analysis** Intention-to-treat analysis on all patients who received dose of study medication ANCOVA analysis undertaken to allow for stratification Analysis undertaken on Change from baseline Numbers log transformed due to skewed data, but not for pH monitoring **Outcomes**	(16.07); 0.60 (14.31): end 20.05 (21.13); 16.86 (15.90) Irritability/crying/fussing: change -0.05 (17.27); -0.61 (22.85); end 88.83 (19.84); 88.85 (20.18) Bradycardia: change 0.81 (7.13); -0.62 (3.26): end 3.01 (7.43); 1.12 (1.82) Oxygen desaturation: change -21.62 (71.23); -21.14 (36.39): end 34.14 (70.76); 41.86 (68.10) Apnea: change change -0.41 (1.73); -1.87 (5.66): end 0.28 (0.90); 0.58 (1.35) Adverse events: 6; 9	on NICU.
Full citation Hussain,S., Kierkus,J.,	**Sample size** 427 infants assessed in 69	**Interventions** Rabeprazole (5 mg per	**Details** **Ethics approval**	**Results** **Outcome: placebo;**	**Limitations** - Method of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Hu,P., Hoffman,D., Lekich,R., Sloan,S., Treem,W., Safety and Efficacy of Delayed Release Rabeprazole in 1- to 11-Month-Old Infants With Symptomatic GERD, Journal of Pediatric Gastroenterology and Nutrition, 58, 233-243, 2014 **Ref Id** 306339 **Country/ies where the study was carried out** USA & other countries **Study type** Multi-centered Double-blind placebo-controlled trial **Aim of the study** Efficacy and safety of raberprazole were studied in infants with GERD **Study dates** Not provided	centers in 10 countries 344 entered open label part of study 268 randomised to treatment 231 completed the study **Characteristics** **Characteristic: placebo; raberprazole 5 mg; raberprazole 10mg; raberprazole total** Number: 90; 90; 88; 178 Mean Age (SD), months: 4.7 (2.65); 4.6 (2.57); 4.7 (2.52); 4.7 (2.54) Male infants (%): 53, 58, 72, 62 Mean weight (SD), kg: 6.5 (1.82); 6.6 (1.61); 6.6 (1.5); 6.5 (1.55) **Inclusion criteria** Aged 1 to 11 months Investigator determined GERD - recurrent vomiting or regurgitation unresponsive to conservative treatment plus either poor weight gain, irritability, excessive crying, sleep distrubance, refusal to eat or back arching. I-GERQ-R score of >16 at screenig for study enrolment whilst not taking acid reduction medication Responded to PPI treatment in open 14 day open label treatment period prior to randomisation	day) for 5 weeks Rabeprazole (10 mg per day) for 5 weeks Placebo for 5 weeks Other PPIs or H2RAs discontinued 3 days prior to trial. Use of drugs affecting gatsrointestinal motility or trial drug was prohibited. Continued use of conservative management strategies was permitted - thickened feeds etc.	Ethics approval gained and informed consent obtained **Randomisation** Not described in detail **Blinding** Not described in detail **Statistical analysis** Sample size based on difference in frequency of regurgitation of 1.5 with SD 3.7 with alpha for 0.05. Sample size of 216 or 72 per arm. ANCOVA used to allow for center comparison **Treatment compliance** Patient took <80% or >120% of scheduled medication **Outcomes** - Frequency of regurgitation - Weight for age z-score - I-GERQ-R weekly score - I-GERQ-R daily score - Adverse events	**rabeprazole** - Frequency of regurgitation: -0.79 vs -1.2 times per day, p = 0.168 - Weight for age z-score: 0.11 vs 0.14, p = 0.440 - I-GERQ-R weekly score: -3.6 vs -3.9, p = 0.960 - I-GERQ-R daily score: -1.87 vs 1.85, p = 0.968 - At least 1 adverse event reported: 47% vs 47%	randomisation and blinding not described in detail - High dropout rate - No washout period be open label and blinded part of study **Other information** - Generalisibility of results to the general population as only children who responded to treatment were randomised.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Janssen R&D	**Exclusion criteria** Known history of acute life-threatening events Milk protein allergy Eosinophilic esophagitis Allergic gastroenteropathy Organ disease Pyloroc stenosis Allergy to PPIs Breast fed infants whose mother was taking PPIs				

I.9 How effective is fundoplication surgery in the treatment of GOR or GORD?

All study types.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Diaz,D.M., Gibbons,T.E., Heiss,K., Wulkan,M.L., Ricketts,R.R., Gold,B.D., Antireflux surgery outcomes in pediatric gastroesophageal reflux disease, American Journal of Gastroenterology, 100, 1844-1852, 2005 **Ref Id** 236936 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To specifically characterize the risk factors associated with fundoplication reoperation, and to compare the short-term outcome for LNF and ONF. **Study dates** From January 1, 1997 to	**Sample size** 456 children: 150 underwent ONF, and 306 underwent LNF. **Characteristics** Gender, female/male, n ONF: 69/81 LNF: 121/185 Age in months at initial operation, median (Range) ONF: 5.5 (1-60) LNF: 7 (1-60) Age in months at initial operation in children with reflux alone, median (Range) ONF: 7 (2-39) LNF: 7 (1-60) Interim to reoperation in months, mean (SD) ONF: 17.16 (8.86) LNF: 11.18 (9.24) Distribution of underlying diagnoses, n/N Reflux alone: ONF: 15/150 LNF: 78/306 Neurologic impairment, n/N	**Interventions** ONF versus LNF -Five pediatric surgeons performed fundoplication	**Details** Consent Not applicable Setting Children's healthcare of Atlanta, Egleston Children's Hospital, Atlanta Methods -Data from the hospital course and long-term surgical outcomes were retrieved from hospital charts and electronic medical records -Mean follow-up time was 36.2 months (SD: 10.9) Statistic methods **For short-term outcomes-complications** -Fisher's exact test for parametric variables -Wilcoxon rank-sum test for nonparametric variables **For long-term outcome-reoperation** **-Multiple logistic regression was used to assess association between the type of initial procedure and the long-term risk of reoperation**	**Results** **Change in frequency of overt regurgitation (e.g., complete cessation, symptom free days, number of episodes per day)** Not reported **Resolution of erosive oesophagitis (endoscopic and histologic)** Not reported **Resolution of reflux symptoms (e.g., heartburn, retrosternal or epigastric pain, waterbrash)** Not reported **Resolution of faltering growth** Not reported **Parent reported reduction in infant distress** Not reported **Oesophageal reflux measured using oesophageal pH-metry** Not reported **Adverse outcomes:** **Patients undergoing reoperation, n/N, (%); OR**	**Limitations** NICE guidelines manual 2012: Appendix D: Methodology checklist: cohort studies A. Selection bias (systematic differences between the comparison groups) A.1 The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome(s) under study)-No A.2 Attempts were made within the design or analysis to balance the comparison groups for potential confounders-No (except for the potential risk factor [LNF vs ONF] for the outcome of reoperation) A.3 The groups were comparable at baseline, including all major confounding and prognostic factors-No Level of risk-High B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation) B.1 The comparison groups received the same care apart from the intervention(s) studied-No

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December 31, 2002 **Source of funding** Partly supported by the National Institute of Health (NIH)	ONF: 50/150 LNF: 98/306 <u>Prematurity, born at 30-36 gestational weeks, n/N:</u> ONF: 19/150 LNF: 41/306 <u>Prematurity, born at <=29 gestational weeks, n/N:</u> ONF: 23/150 LNF: 54/306 <u>Cardiac disease, n/N:</u> ONF: 30/150 LNF: 47/306 <u>Respiratory disease, n/N:</u> ONF: 55/150 LNF: 135/306 **Inclusion criteria** -Children with ages ranging from new-borns to 60 months, who underwent Nissen fundoplication during the period of January 1997 to December 31, 2002. **Exclusion criteria** -Children with incomplete preoperative data; -Acute conversion from LNF to ONF; -Children with underlying		-**Independent variables:** initial operation type (LNF vs ONF), age category at initial operation, gender, neurological impairment, chronic respiratory conditions, cardiac disease, history of prematurity, and history of reflux alone. -**Confounders adjusted for**: possible confounding effects of age at initial operation, and patients comorbidities that were related to the risk of reoperation in previous studies were adjusted for. -Odds ratios and 95% confidence intervals (CI) were used to estimate the effect of independent variables on reoperation; these measures of association were estimated before and after adjustment by using the logistic regression procedure; **-Survival analysis (survival was defined as patients who did not require reoperation)** Survival analysis was performed by the Kaplan-Meier method to estimate reoperation rates for ONF and LNF, with comparisons based on the two-sided log-rank test, and significance	**<u>(95% CI), *P* value</u>** LNF: 43/306 (14%), ONF: 12/150 (8%) LNF versus ONF: 1.88 (0.96-3.68), *P* = 0.06 **<u>Frequency of short-term adverse outcomes, n (%), P values</u>** -Acute bleeding: LNF: 1 (0.8%), ONF: 0, P=0.67 -Acute respiration problem: LNF: 4 (1.3%), ONF: 12 (8%), P=0.046 -Acute infection: LNF: 3 (0.9%), ONF: 2 (1.3%), P=0.53 -Acute prolonged ileus: LNF: 4 (1.3%), ONF: 14 (9.3%), P=0.0003 -Acute other: LNF: 6 (1.9%), ONF: 6 (4%), P=0.2 -Total acute complications: LNF: 18 (5.9%), ONF: 34 (22.7%), P=0.0001 **<u>Potential risk factors for reoperation (long-term), OR (95% CI), P values</u>** -Initial operation type (LNF vs ONF): 1.68 (0.84-3.3), P=0.1427 -Age 0-5 months: 1.08 (0.52-2.2), P=0.8276	B.2 Participants receiving care were kept 'blind' to treatment allocation-No B.3 Individuals administering care were kept 'blind' to treatment allocation-No Level of risk: High <u>C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants</u> C.1 All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)-Yes C.2a How many participants did not complete treatment in each group?-N/A C.2b The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)-N/A C.3a For how many participants in each group were no outcome data available?-N/A C.3b The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)-N/A Level of risk: Low <u>D. Detection bias (bias in how outcomes are ascertained,</u>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	congenital anatomic anomalies of the esophagus;		level at P<0.05; **Follow-up** -Mean follow-up time was 36.2 months (SD: 10.9)	-Age 6-11 months: 1.12 (0.5-2.5), P=0.7862 -Gender (male vs female): 0.73 (0.41-1.3), P=0.73 -Neurological impairment: 1.35 (0.62-2.9), P=0.4409 -Chronic respiratory condition: 1.30 (0.7-2.4), P=0.4069 -Cardiac disease: 0.78 (0.28-2.1), P=0.6384 -Prematurity: 1.48 (0.7-3.1), P=0.3117 -Reflux alone: 2.04 (0.78-5.4), P=0.1477 -Difference in survival (defined as those who did not require reoperation) 1) Reported as Kaplan-Meier curves of the cumulative probability of reoperation in subjects who underwent LNF or ONF. Mean follow-up time 36.1 months, SD: 10.96, range (12.9-59.8) A significant difference in reoperation was observed between LNF and ONF, with a log-rank X^2 (1 d f)=5.44, P=0.01 2) Reported as comparison of the probability of survival and respective reoperation rate at 12, 24, and 36 months, survival	diagnosed or verified) D.1 The study had an appropriate length of follow-up-Unclear D.2 The study used a precise definition of outcome-No (not for reported adverse outcomes) D.3 A valid and reliable method was used to determine the outcome-Unclear D.4 Investigators were kept 'blind' to participants' exposure to the intervention-No D.5 Investigators were kept 'blind' to other important confounding and prognostic factors-No Level of bias: High **Indirectness** Does the study match the review protocol in terms of; Population: Yes Outcome: Yes Indirectness: Some **Other information** 1) The retrospective design of the study: information obtained by such study is not controlled, may be incomplete, and have inaccuracies. 2) There could be other unmeasured confounders, for example, operations were

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				(reoperation %) 12 months: LNF: 89.5 (10.5), ONF: 96 (4.0) 24 months: LNF: 86.6 (13.4), ONF: 93.3 (6.7) 36 months: LNF: 85.6 (14.4), ONF: 91.9 (8.1) Cumulative total: LNF: 85.9 (14.1), ONF: 92 (8.0) **Improvement in validated reflux questionnaire** Not reported **Parent satisfaction with the intervention** Not reported	performed by a group of five surgeons, personal technique and experience with either ONF or LNF are variables that are not standardized or surgical procedure approach protocolised
Full citation Knatten,C.K., Fyhn,T.J., Edwin,B., Schistad,O., Emblem,R., Bjornland,K., Thirty-day outcome in children randomized to open and laparoscopic Nissen fundoplication, Journal of Pediatric Surgery, 47, 1990-1996, 2012 **Ref Id** 250065 **Country/ies where the study was carried out** Norway **Study type** RCT	**Sample size** -107 patients accepted for primary anti-reflux surgery, 88 entered the study and were randomized. -44 to the Open Nissen Fundoplication group (ONF), 44 to the Laparoscopic Nissen Fundoplication group (LNF) **Characteristics** **Gender, boy/girl, n** ONF: 31/13 LNF: 25/19 **Presence of scoliosis, n/N** ONF: 5/44 LNF: 7/44 **Neurologic impaired,**	**Interventions** ONF versus LNF -Both ONF and LNF were done according to strict surgical and anesthesiology guidelines, and procedures were performed identically, except from the approach of laparotomy or laparoscopy -Taking down or establishment of gastrostomy in addition to fundoplication was performed in both groups Taking down of preoperative	**Details** Consent Informed written consent obtained from parents Setting Two tertiary hospitals (referral centres) in Norway, one in Ulleval and the other one in Rikshospitalet Randomisation method block randomisation (randomisation was done in blocks of 10, blocks were not stratified) Concealment of allocation Not reported Comparability of intervention groups at baseline	**Results** **Change in frequency of overt regurgitation (e.g., complete cessation, symptom free days, number of episodes per day)** Not reported **Resolution of erosive oesophagitis (endoscopic and histologic)** Not reported **Resolution of reflux symptoms (e.g., heartburn, retrosternal or epigastric pain, waterbrash)** Not reported **Resolution of faltering growth** Not reported	**Limitations** NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials A Selection bias A1 - Was there appropriate randomisation - Yes A2 - Was there adequate concealment - No A3 - Were groups comparable at baseline - Yes Level of bias: Unclear B Performance bias B1 - Did groups get same level of care - Unclear B2 - Were participants blinded to treatment allocation- No B3 - Were individuals administering care blinded to treatment allocation- No Level of bias: High

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
-not blinded pre- or postoperatively **Aim of the study** To compare the effectiveness of Open Nissen Fundoplication versus Laparoscopic Nissen Fundoplication in treating gastroesophageal reflux disease in children. **Study dates** January 2003 to January 2007 **Source of funding** Not reported	**Yes/No, n** ONF: 23/21 LNF: 23/21 **Preoperative gastrostomy, Yes/No, n** ONF: 18/26 LNF: 20/24 **Age in years, median (range)** ONF: 3.5 (0.1-14.2) LNF: 4.7 (0.2-15.4) **Days at tertiary hospital, median (range)** ONF: 6.0 (2-9) LNF: 4.5 (2-21) **Total hospital (tertiary & local) days, median (range)** ONF: 7.5 (2-20) LNF: 7.0 (3-57) **Inclusion criteria** Not reported **Exclusion criteria** -Age greater than 15 years at referral -Parents that did not speak Norwegian -Multiple previous laparotomies -Comorbidity assessed to be incompatible with laparoscopy	gastrostomy: ONF, n=2; LNF, n=3 Establishment of gastrostomy: ONF, n=6; LNF, n=5 -Three patients had minor procedures in addition to fundoplication. They were adenectomy, insertion of ear tube, and esophageal endoscopy with dilation. There were no complications related to these minor procedure.	The two groups were comparable in terms of age, weight, and comorbidity at baseline, there were no significantly differences between them Blinding Lack of blinding in both clinical staff and patients Statistical methods -Sample size calculation For the primary outcome of the study, which was recurrence of GER, it reported that the necessary number of patients determined by the power calculation was not reached. For complication rates (adverse outcomes): a post hoc power calculation was performed with power set 80% and significance level 5%. For a sample size of 88 patients, the minimum difference in complication rate that could have been detected was 30%, corresponding to 24 patients with complication in one group and approximately 15 in the other group. Furthermore, a sample size of at least 310 included patients would be necessary to obtain a significant result of the grade IIIb complications occurring in 6 (13.6%) LNF patients and 2	**Parent reported reduction in infant distress** Not reported **Oesophageal reflux measured using oesophageal pH-metry** Not reported **Adverse outcomes, n** Reported as postoperative complications occurring in the first 30 days after ONF or LNF -Patients with complications: n/N ONF: 24/44, LNF: 24/44 -Grade I complications, n (number of complications, graded according to the Clavien-Dindo classification complications) Total number: ONF-11, LNF-11 Dislocated gastrostomy: ONF-0, LNF-1 Hematoma at the epigastric post site: ONF- 0, LNF-1 Gastroenteritis: ONF-1, LNF-1 Wound infection: ONF-1, LNF-0 Feeding problems: ONF-9, LNF-8 -Grade II complications, n (number of complications, graded according to the Clavien-Dindo classification complications) Total number: ONF-18, LNF-17	C Attrition bias C1 - Was follow-up equal for both groups - Yes C2 - Were groups comparable for dropout - Yes C3 - Were groups comparable for missing data - Yes Level of bias: Low D Detection bias D1 - Was follow-up appropriate length - Unclear D2 - Were outcomes defined precisely - Yes D3 - Was a valid and reliable method used to assess outcome - Unclear D4 - Were investigators blinded to intervention - No D5 - Were investigators blinded to confounding factors - No Level of bias: Unclear Indirectness Does the study match the review protocol in terms of Population: yes Intervention: yes Outcomes: yes Indirectness: no **Other information** **1) The study was not adequately powered for the primary outcome of recurrence of GER, it reported that the necessary number of patients**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	-Need of urgent operation and no time for randomization -Unwillingness to participate		(4.5%) ONF patients. -Intention to treat analysis Not reported <u>Follow-up</u> -Complications during surgery, surgeon performing the procedure, and complications occurring the first 30 postoperative days were recorded -In the 30-day period after surgery, discharge summaries from the local hospitals were obtained to register any further postoperative complication and readmissions	Airway complications: ONF-14, LNF-8 Gastrostomy infection: ONF-1, LNF-6 Blood transfusion: ONF-2, LNF-2 Urinary tract infection: ONF-1, LNF-0 Gastroenteritis: ONF-0, LNF-1 -Grade III complication, n (number of complications, graded according to the Clavien-Dindo classification complications) Total number: ONF-2, LNF-6 Food impaction: ONF-1, LNF-2 Port site hernia/wound rupture: ONF-1, LNF-2 Redo gastrostomy: ONF-0, LNF-2 -Total number of complications: ONF-31, LNF-34 -Patients readmitted to their local hospitals because of complications after discharge: ONF-11, LNF-12 **<u>Improvement in validated reflux questionnaire</u>** Not reported **<u>Parent satisfaction with the intervention</u>** Not reported	**determined by the power calculation was not reached. For adverse outcomes, a post hoc power calculation was performed.** 2) Indication for fundoplication was symptoms of GER disease despite optimal medical anti-reflux therapy. Patients were verified by 24-hour pH monitoring and/or an upper gastrointestinal contrast study.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation McHoney,M., Wade,A.M., Eaton,S., Howard,R.F., Kiely,E.M., Drake,D.P., Curry,J.I., Pierro,A., Clinical outcome of a randomized controlled blinded trial of open versus laparoscopic Nissen fundoplication in infants and children, Annals of Surgery, 254, 209-216, 2011 **Ref Id** 219208 **Country/ies where the study was carried out** UK **Study type** Double-blinded randomized controlled trial -Parents and postoperative staff were blinded to allocation **Aim of the study** To compare the clinical outcome in children undergoing Nissen fundoplication who were randomized to laparotomy or laparoscopy, and to quantify any difference in the endocrine response between approaches.	Sample size 44 patients were randomized, 21 to the open, 23 to the laparoscopy (20 from the open group and 19 from the laparoscopy group received the allocated intervention and were included in the analysis) **Characteristics** **Age in months, median (interquartile range)** Open: 47.6 (7.9-100.9) Laparoscopic: 66.9 (20.89-126.2) **Weight in kilograms, median (interquartile range)** Open: 12.8 (7.4-18.3) Laparoscopic: 14.5 (9.8-23.0) **Neurological impairment n/N (percentage)** Open: 15/20 (75%) Laparoscopic: 15/19 (79%) **Congenital anomaly n/N (percentage)** Open: 0 Laparoscopic: 1/19 (5%) **Inclusion criteria** -Children over 1 month of age undergoing Nissen fundoplication for gastro-	**Interventions** Open Nissen Fundoplication (ONF) versus Laparoscopic Nissen Fundoplication (LNF) -Nissen fundoplication, with or without gastrostomy, was performed using standard techniques.	**Details** Consent Parents were give full informed consent Setting Royal hospital for Sick Children, Edinburgh Sample size calculation -Resting energy expenditure data obtained from previous studies children was used in the power calculation (resting energy expenditure was the primary outcome measure of the trial) -Detection of a difference of 1 standard deviation in the 4-hour postoperative resting energy expenditure level between groups, using 5% as the significance level, required 16 and 21 patients per group for 80% and 90% power, respectively. The study therefore aimed to recruit 40 patients (not powered for the clinical outcomes) Methods -Operative technique was standardized between both limbs of the trial -Postoperative management was a standardized protocol with a feeding regimen -Validated tool was used for	**Results** **Change in frequency of overt regurgitation (e.g., complete cessation, symptom free days, number of episodes per day)** -Reported as late postoperative recurrence, n/N (%); Difference (95% CI): ONF: 3/18 (16.7%), LNF 1/14 (7.1%); 9.5% (-17.1, 32.8) **Resolution of erosive oesophagitis (endoscopic and histologic)** Not reported **Resolution of reflux symptoms (e.g., heartburn, retrosternal or epigastric pain, waterbrash)** Not reported **Resolution of faltering growth** Not reported **Parent reported reduction in infant distress** Not reported **Oesophageal reflux measured using oesophageal pH-metry** Not reported **Adverse outcomes, n/N (%); Difference (95% CI)** -Mean time to full feed in days, mean (CI): ONF: 2 (2-4), LNF: 2 (2-4), P =	**Limitations** NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials A Selection bias A1 - Was there appropriate randomisation - Yes A2 - Was there adequate concealment - Yes A3 - Were groups comparable at baseline - Yes Level of bias: low B Performance bias B1 - Did groups get same level of care - Yes B2 - Were participants blinded to treatment allocation- Yes B3 - Were individuals administering care blinded to treatment allocation- Yes, postoperatively Level of bias: Low C Attrition bias C1 - Was follow-up equal for both groups – Yes C2 - Were groups comparable for dropout - Yes (except for the outcome of recurrence and retching; 5 out of 19 (26%) and 3 out of 19 (16%) of patients dropped out in the LNF arm, respectively, reasons not reported) C3 - Were groups comparable for missing data - Yes (except for the outcome of recurrence and retching, reasons not reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Not reported **Source of funding** Supported by Sport Aiding medical Research for Kids (SPARKS)	oesophageal reflux -All patients were investigated for reflux according to the RCT's protocol, depending on clinical presentation -Reflux was documented by pH study, contrast study, endoscopy or a combination of the three. **Exclusion criteria** -patients with sepsis, multi-organ dysfunction syndrome, cardiac, renal, immunological or metabolic abnormalities -Children requiring O2 therapy		the postoperative pain assessment and analgesia; pain was blindly assessed by nurses and the acute pain team <u>Randomisation methods</u> Minimization, criteria were: -age (1 month to 3 years, 3-6 years, and >6 years) -neurological status (normal, impaired) -operating surgeon, and -presence/absence of major congenital gastrointestinal abnormities <u>Concealment of allocation</u> Not reported <u>Comparability of groups at baseline</u> Groups were comparable with respect to weight and the minimization criteria used <u>Blinding</u> -Postoperatively parents, laboratory staff, acute pain team nurses, and ward nurses were blinded to patients allocation -An occlusive dressing was used to hide the operative site in the postoperative period <u>Follow-up</u> -Early postoperative outcomes occurring the first 4 days were recorded;	0.85 -Early postoperative incidence of infection: ONF: 1/20 (5%), LNF: 3/19 (16%); -10.8% (-33, 10.5) -Early postoperative incidence of gastric paresis: ONF: 2/20 (16%), LNF: 3/19 (11%); -5.8% (-28.7, 16.8) -Early postoperative morphine requirement: Reported as the rate of fall in morphine requirement: "The rate of fall was not significantly different between the 2 groups (-.061) [-3.45, 2.20] per day in the laparoscopy compared with open, P=0.67" (average or mean rate of fall in each group was not reported) -Late postoperative incidence of dysphagia: ONF: 0/16 (0%), LNF: 1/16 (6.3%); -6.3% (-28.3, 13.8) -Late postoperative incidence of retching: ONF: 10/18 (55.6%), LNF: 1/16 (6.3%); 49.3% (18.3, 69.8) **<u>Improvement in validated reflux questionnaire</u>** Not reported **<u>Parent satisfaction with the intervention</u>** Not reported	Level of bias: Low D Detection bias D1 - Was follow-up appropriate length - Unclear D2 - Were outcomes defined precisely - No D3 - Was a valid and reliable method used to assess outcome - Unclear (the outcome of retching was a subjective outcome reported by the parents postoperatively) D4 - Were investigators blinded to intervention - Not all, the postoperative staff were blinded D5 - Were investigators blinded to confounding factors -Not all, the postoperative staff were blinded Level of bias: Unclear Indirectness Does the study match the review protocol in terms of Population: yes Intervention: yes Outcomes: yes Indirectness: some **Other information** **-The study was not powered for the clinical outcomes (primary outcome measure of the trial was resting energy expenditure between patients undergoing LNF and those**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			-Patients were prospectively followed in outpatients department (with regard to report of recurrence of vomiting and presence of retching); -Late postoperative clinical outcome, median length of follow-up was 22 (range 12-34) months. Statistical methods -Intention to treat analysis: not performed (as the aim of the study was to assess the effects of the actual operation performed) -T-test and Mann-Whiney U tests were used to compare continuous outcomes between randomisation groups		**undergoing ONF)** -Children over 1 month of age undergoing Nissen fundoplication for gastro-oesophageal reflux were approached for inclusion in this trial. All patients were investigated for reflux according to the trial's protocol, depending on clinical presentation. Reflux was determined by pH study, contrast study, endoscopy or a combination of the three. -Median follow-up time was 22 (range 12-34) months. The time points for postoperative clinical outcomes were not clearly reported. -The study reported that there was significantly more retching in the open group. However, it should be noted that reporting of retching was a subjective assessment made by the parents or carers, who were no longer blinded and is open to bias.
Full citation Srivastava,R., Downey,E.C., O'Gorman,M., Feola,P., Samore,M., Holubkov,R., Mundorff,M., James,B.C., Rosenbaum,P., Young,P.C., Dean,J.M., Impact of fundoplication versus gastrojejunal feeding tubes on mortality and in	**Sample size** 366 children with neurologic impairment and gastroesophageal reflux disease -43 had a first gastrojejunal feeding tube -323 underwent a first fundoplication **Characteristics** Age at time of procedure in	**Interventions** Fundoplication versus gastrojejunal feeding tubes (GJT)	**Details** Consent: Not reported Setting: Primary Children's Medical Centre (PCMC), which serves as a tertiary referral hospital for 5 states. Sample size calculation: Not reported	**Results** **Change in frequency of overt regurgitation (e.g., complete cessation, symptom free days, number of episodes per day)** Not reported **Resolution of erosive oesophagitis (endoscopic and histologic)** Not reported	**Limitations** NICE guidelines manual 2012: Appendix D: Methodology checklist: cohort studies A. Selection bias (systematic differences between the comparison groups) A.1 The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
preventing aspiration pneumonia in young children with neurologic impairment who have gastroesophageal reflux disease, Pediatrics, 123, 338-345, 2009 **Ref Id** 246256 **Countr/ies where the study was carried out** USA **Study type** Retrospective, observational cohort study **Aim of the study** To compare outcomes for children with neurological impairment and gastroesophageal reflux disease after either a first fundoplication or a first gastrojejunal feeding tube (GJT). **Study dates** Between January 1997 and December 2005 **Source of funding** The project was partly	months, mean (SD), month Fundoplication: 16 (16) GJT: 24 (20) P=0.008 Gender (female), n (%), P Fundoplication: 146 (45) GJT: 13 (30) P=0.07 Previous aspirational pneumonia, n (%), P Fundoplication: 50 (15) GJT: 9 (21) P=0.36 Tracheostomy, n(%), P Fundoplication: 21 (7) GJT: 9 (21) P<0.001 Previous swallow study, n(%), P Fundoplication: 196 (61) GJT: 29 (67) P=0.38 Cerebral spinal fluid shunt, n(%), P Fundoplication: 38 (12) GJT: 12 (28) P=0.004 Chronic lung disease, n(%), P Fundoplication: 50 (15) GJT: 7 (16) P=0.89 Seizures, n (%), P Fundoplication: 117 (36) GJT: 21 (49)		Methods: -Patients were identified using Intermountain Health-care's Enterprise Data Warehouse, an organized and integrated administrative database that stores 8 million patients encounters and includes clinical, laboratory, and radiologic data from all inpatients and outpatients settings and uses a linked unique identifier for each individual patient. Statistical methods: -X^2 or Fisher's exact tests was used to compare the categorical variables; -the 2-tailed, unpaired t-test, or Wilcoxon rank-sum test was used to compare continuous variables; -Bivariate and multivariate Cox proportional hazards regression analyses were used to determine the association of fundoplication with mortality; These Cox models were adjusted for heterogeneity, defined as baseline variables that were associated with mortality and clinically significant variables; -Survival curves were constructed using Kaplan-Meier estimates with comparisons between curves based on the log rank statistic;	**Resolution of reflux symptoms (e.g., heartburn, retrosternal or epigastric pain, waterbrash)** Not reported **Resolution of faltering growth** Not reported **Parent reported reduction in infant distress** Not reported **Oesophageal reflux measured using oesophageal pH-metry** Not reported **Adverse outcomes, n/N, HR (95% CI, P value)** Reported as: Survival time It reported that there was no difference in survival or time to aspiration pneumonia between the two groups in the unadjusted Cox proportional hazards analyses Death (fundoplication versus GJT) during the follow-up time (10 years, median 3.4 years) Fundoplication: 40/323 (12%), GJT: 9/43 (21%) -Heterogeneity adjusted model: 0.55 (0.25-1.21; P=0.14) -Propensity adjusted model: 0.49 (0.23-1.03; P=0.06) -Age stratified propensity adjusted model, patients > 1	not expected to affect the outcome(s) under study)-No A.2 Attempts were made within the design or analysis to balance the comparison groups for potential confounders-Yes A.3 The groups were comparable at baseline, including all major confounding and prognostic factors-No Level of bias: High B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation) B.1 The comparison groups received the same care apart from the intervention(s) studied-Unclear B.2 Participants receiving care were kept 'blind' to treatment allocation-No B.3 Individuals administering care were kept 'blind' to treatment allocation--No Level of bias: High C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants C.1 All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)-Yes C.2a How many participants did not complete treatment in each group?-N/A C.2b The groups were comparable for treatment

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
supported by the Children's Health Research Centre at the University of Utah and Primary Children's Medical Centre Foundation	P=0.11 Specific conditions with relative surgical contraindications, n (%), P Fundoplication: 28 (9) GJT: 12 (28) P<0.001 Clinical Classification Code Cardiovascular, n(%), P Fundoplication: 27 (63) GJT: 139 (43) P=0.014 Respiratory, n(%), P Fundoplication: 85 (26) GJT: 14 (33) P=0.38 Renal, n(%), P Fundoplication: 16 (5) GJT: 5 (12) P=0.08 Gastrointestinal, n (%), P Fundoplication: 22 (7) GJT: 9 (21) P=0.002 Hematology or immunologic, n (%), P Fundoplication: 5 (2) GJT: 1 (2) P=0.71 Metabolic, n (%), P Fundoplication: 29 (9) GJT: 5 (12) P=0.57 Other congenital or genetic defect, n (%), P		-Because patients were not randomly assigned to GJT or fundoplication surgery, potential confounding by indication was adjusted for by developing a propensity score for fundoplication surgery treatment. -Propensity score was created by stepwise logistic regression analyses, which selected baseline variables that were associated with fundoplication. Variables that were clinically relevant but not significant in the initial logistic regression analyses were then added to derive a full non-parsimonious model. This model yielded a concordance index of 0.78, indicating a strong ability to differentiate between patients undergoing GJT versus fundoplication; -Using these selected baseline variables, a propensity score for undergoing a fundoplication was estimated by maximum likelihood logistic regression analysis. This score ranged from 0.23 to 0.98 and reflected the probability that a patient would undergo a fundoplication. -Additional cox proportional hazards analyses were adjusted for confounding by using propensity scores as a variable in the models;	year of age versus patients <=1 year of age: 0.30 (0.12-0.73, P=0.008) Aspirational pneumonia (fundoplication versus GJT) during the follow-up time (10 years, median 3.4 years) Fundoplication: 48/323 (15%), GJT 7/43 (16%) -Propensity adjusted model: 0.71 (0.21-1.69, P=0.44) -It stated that none of the models revealed significance, detailed results for other models were not reported; **Improvement in validated reflux questionnaire** Not reported **Parent satisfaction with the intervention** Not reported	completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)-N/A C.3a For how many participants in each group were no outcome data available?-N/A C.3b The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)-N/A Level of bias: Unclear D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified) D.1 The study had an appropriate length of follow-up-Yes D.2 The study used a precise definition of outcome-Yes (defined by ICD-9-CM) D.3 A valid and reliable method was used to determine the outcome-No (detailed data on mortality were available for <60% of patients; cause of aspiration pneumonia could not be determined) D.4 Investigators were kept 'blind' to participants' exposure to the intervention-No D.5 Investigators were kept 'blind' to other important confounding and prognostic factors-No

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Fundoplication: 124 (38) GJT: 24 (56) P=0.028 Malignancy, n (%), P Fundoplication: 6 (2) GJT: 3 (7) P=0.04 Reasons for neurologic impairment Cerebral palsy, n (%), P Fundoplication: 165 (42) GJT: 20 (47) P=0.55 Brain or spinal cord anomaly, n (%), P Fundoplication: 122 (38) GJT: 20 (47) P=0.26 Hydrocephalus, n (%), P Fundoplication: 66 (20) GJT: 14 (33) P=0.07 Chromosomal anomalies, n (%), P Fundoplication: 50 (15) GJT: 11 (26) P=0.09 Cerebral degeneration, n (%), P Fundoplication: 42 (13) GJT: 3 (7) P=0.26 Down syndrome, n (%), P Fundoplication: 37 (11) GJT: 2 (5)		Follow-up time -From January 1997 to October 2006; median length of follow-up until death or October 2006 was 3.4 years.		Level of bias: High **Indirectness** Does the study match the review protocol in terms of; Population: Yes Outcome: Yes Indirectness: Some **Other information** 1) Propensity scores were used to in an attempt to overcome potential confounding by indications. However, this method is limited when there are unmeasured variables that may influence the choice between either a GJT or a fundoplication; 2) Only patients born after January 1997 were included, this may affect the generalizability of the study results; 3) Aspiration pneumonia may have continued to be caused by primary aspiration (e. g, of secretions) and not secondary aspiration (e. g, refluxed gastric contents). Only a limited group of children had a swallow study in their evaluation before a first procedure to diagnose primary aspiration; it is possible that a child with neurological impairment may develop primary aspiration depending on the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	P=0.18 Nervous system anomaly, n (%), P Fundoplication: 30 (9) GJT: 6 (14) P=0.33 Muscular dystrophy or myopathy, n (%), P Fundoplication: 24 (7) GJT: 2 (5) P=0.51 Other paralytic conditions, n (%), P Fundoplication: 21 (6) GJT: 5 (12) P=0.22 Anterior horn cell, n (%), P Fundoplication: 20 (6) GJT: 1 (2) P=0.31 Spina bifida, n (%), P Fundoplication:14 (4) GJT: 4 (9) P=0.16 Mental retardation, n (%), P Fundoplication: 12 (4) GJT: 0 (0) P=0.20 Demyelinating central nervous system disorders, n (%), P Fundoplication: 3 (1) GJT: 1 (2) P=0.41				cause of their neurologic impairment. Given the retrospective nature of the study, the distinction between primary and secondary aspiration could not be made; 4) Because of the retrospective nature of the study, whether either treatment group continued with oral intake could not be determined. If continued oral intake were more common in one of the groups it could contribute to differences in the frequency of pneumonia not attributable to the procedure; 5) Detailed data on mortality were available for <60% of patients (given how many died out of hospital). No functional limitations adjustment could be performed because of lack of information in the database; 6) The study was underpowered for the outcome of death

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Spinocerebellar disease, n (%), P Fundoplication: 1 (0.3) GJT: 2 (5) P=0.003 Tuberous sclerosis, n (%), P Fundoplication: 1 (0.3) GJT: 0 (0) P=0.72 Infantile spasms, n (%), P Fundoplication: 17 (5) GJT: 4 (9) P=0.28 Aspirational pneumonia (outcome), n (%), P Fundoplication: 48 (15) GJT: 7 (16) P=0.65 Death (outcome), n (%), P Fundoplication: 40 (12) GJT: 9 (21) P=0.12 **Inclusion criteria** 1) date of birth between January 1, 1997, and December 31, 2005; 2) having a previously published International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for neurological impairment with the additions of demyelinating central nervous system conditions (340-341.9),				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	other paralytic conditions (344.0-344.9), spina bifida (741.0-741.93), spinocerebellar disease (334.0, 334.9), and tuberous sclerosis (759.5) either on the data of the procedure or in any previous encounter with Intermountain Health care; 3) Diagnosis of GERD (defined by ICD-9-CM codes 530.11 or 530.81), either on the date of procedure or in any previous encounter, and 4) having either a first fundoplication (44.66, 44.67) performed or a first GJT (internal charge code) placed between January 1, 1997, and December 31, 2005, at Primary Children's Medical Centre (PGMC) **Exclusion criteria** 1) patients with neurological impairment who had GERD but neither study procedure (and only medical management with acid suppression or prokinetic agents); 2) patients who were born before January 1, 1997				

I.10 How effective is enteral tube feeding in the management of GOR or GORD?

There was no evidence table for this review.