**Supplemental File 1 – Full Methodology**

Databases of Embase and MEDLINE/PubMed were searched from inception to April 2016 (for full search-strategy see Supplemental File 1). In addition, reference lists of review articles and included studies were searched. No date or language restrictions were applied. The exact reporting guidelines as described in the PRISMA statement ([www.prisma-statement.org](http://www.prisma-statement.org/)) were followed.

## Study selection

Search results were combined using EndNote software version 7.0 and duplicates were removed. Two investigators (MMT and MWL) independently reviewed identified titles and abstracts of all citations in the literature. Inclusion criteria were: 1. study population 0-18 years; 2. prospective, longitudinal observational study design; 3. one of the aims of the study was to evaluate the prognosis and clinical course of GERD; 4. baseline measurement of at least one of the outcomes of the research population provided and 5. follow-up >8 weeks. Studies were excluded when they concerned GER and not GERD, children with a developmental delay, anatomical abnormality or known underlying organic cause of GERD. Studies with a retrospective/prospective design were included as long as follow-up data of interest (see data extraction) was prospectively collected. All potentially relevant studies, were retrieved as full-text articles. Disagreements between reviewers were adjudicated by discussion and consensus with a third-party arbiter (MMJS).

**Quality assessment**

To assess methodological quality of the included studies, the Quality in Prognostic Studies (QUIPS) tool was used independently by two reviewers (MMT and MWL).(15, 16) The QUIPS tool assesses risk of bias in six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and presentation. Disagreements were resolved through consensus or by arbitration of a third person (MMJS).

**Data extraction**

Two reviewers independently performed a structured data extraction from the original studies, using a standardized data extraction form. Outcomes of interest were determined and presented according to the definition of GERD as GER leading to troublesome *symptoms* (e.g. well-defined typical GERD-related symptoms) and/or endoscopic *complications* (e.g. strictures, Barrett's esophagus, and/or esophageal adenocarcinomaand occurrence or resolution of esophagitis).(1) Quality of life of children and/or parents was selected as an additional outcome of interest. Study characteristics including study setting, design, population, definition of GERD and follow-up results regarding these predetermined outcomes were tabulated and presented descriptively.

**Data analysis**

Large clinical diversity among the included studies with regard to participants, disease definitions, and definition of outcomes existed and different statistical approaches and adjustments for different variables were used. Therefore, we refrained from performing meta-analyses and decided to present study results qualitatively. For consistency, associations were recalculated to be in the same direction, with associations above 1 indicating worse prognosis. If proportions or percentages on outcomes of interest were not provided by the original studies, manual calculations were performed where possible. For dichotomous variables, Χ2-test was performed to calculate missing P-values where possible. P-values <0.05 as reported by the authors were considered statistically significant.

**Full search strategy**

Database(s): **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)**1946 to Present
Search Strategy:

|  |  |  |
| --- | --- | --- |
| **#** | **Searches** | **Results** |
| 1 | (exp \*Gastroesophageal Reflux/ or \*esophagitis/ or \*esophagitis, peptic/ or (gastroesophageal adj reflux).ti,ab. or (gastrooesophageal adj reflux).ti,ab. or (gastro esophageal adj reflux).ti,ab. or (gastro oesophageal adj reflux).ti,ab. or (GORD or GOR or GERD or GER).ti,ab. or (esophagitis or oesophagitis).ti,ab,kw. or (gastric adj3 (acid or reflux)).ti,ab. or (reflux adj (oesophagitis or esophagitis)).ti,ab. or (erosive adj3 (oesophag\* or esophag\*)).ti,ab.) not (\*Esophageal Atresia/ or esophageal atresia.ti.) | 46861 |
| 2 | adolescent/ or child/ or child, preschool/ or infant/ or infant, newborn/ or infant, low birth weight/ or infant, postmature/ or infant, premature/ or exp Pediatrics/ or (child\* or infant\* or infancy or newborn\* or neonat\* or baby or babies or preschool or pre school or pubescen\* or teen\* or adolescen\* or puber\* or prepubert\* or juvenil\* or p?ediatric\* or youth\* or schoolchild\* or school age\* or schoolage\* or preschool or pre-school or elementary school or high school\* or highschool\* or kindergar\* or boy or boys or girl\* or minor\* or underag\* or under ag\* or kid or kids or toddler\*).ti,ab. | 3801993 |
| 3 | Cohort Studies/ or exp Mortality/ or Follow-Up Studies/ or Prognosis/ or survival analysis/ or incidence/ or (incidence or prognos\* or predict\* or course).ti,ab,kw. | 3218669 |
| 4 | (Adult/ or exp Aged/ or adult\*.ti,ab,kw. or elder\*.ti,ab,kw.) not (adolescent/ or exp child/ or exp Pediatrics/ or (child\* or adolescen\* or p?ediatric\*).ti,ab,kw.) | 4331305 |
| 5 | (Animals/ not Humans/) or exp Animals, Laboratory/ or exp Animal Experimentation/ or exp Models, Animal/ or exp Rodentia/ or (rat or rats or mouse or mice or animal\*).ti. or editorial/ or letter/ or news/ or Comment/ or exp historical article/ or Anecdotes as Topic/ or Case Reports/ or (letter\* or comment\* or abstracts).ti. or case report\*.ti,ab,kw. | 8565871 |
| 6 | (1 and 2 and 3) not 4 not 5 | 2384 |

Database(s): **Embase Classic+Embase**1947 to 2016 April 25
Search Strategy:

|  |  |  |
| --- | --- | --- |
| **#** | **Searches** | **Results** |
| 1 | (exp \*gastroesophageal reflux/ or \*esophagitis/ or \*reflux esophagitis/ or ((gastroesophageal adj reflux) or (gastrooesophageal adj reflux) or (gastro esophageal adj reflux) or (gastro oesophageal adj reflux) or (GORD or GOR or GERD or GER)).ti,ab. or (esophagitis or oesophagitis).ti,ab,kw. or (gastric adj3 (acid or reflux)).ti,ab. or (reflux adj (oesophagitis or esophagitis)).ti,ab. or (erosive adj3 (oesophag\* or esophag\*)).ti,ab.) not (\*Esophageal Atresia/ or esophageal atresia.ti.) | 69015 |
| 2 | adolescent/ or child/ or preschool child/ or infant/ or newborn/ or exp low birth weight/ or postmaturity/ or prematurity/ or exp pediatrics/ or (child\* or infant\* or infancy or newborn\* or neonat\* or baby or babies or preschool or pre school or pubescen\* or teen\* or adolescen\* or puber\* or prepubert\* or juvenil\* or p?ediatric\* or youth\* or schoolchild\* or school age\* or schoolage\* or preschool or pre-school or elementary school or high school\* or highschool\* or kindergar\* or boy or boys or girl\* or minor\* or underag\* or under ag\* or kid or kids or toddler\*).ti,ab. | 4222553 |
| 3 | cohort analysis/ or incidence/ or exp mortality/ or follow up/ or exp survival/ or prognosis/ or prediction/ or disease course/ or (incidence or prognos\* or predict\*).ti,ab,kw. | 4798985 |
| 4 | (adult/ or aged/ or adult\*.ti,ab,kw. or elder\*.ti,ab,kw.) not (adolescent/ or child/ or exp pediatrics/ or (child\* or adolescen\* or p?ediatric\*).ti,ab,kw.) | 5330051 |
| 5 | (animal/ not human/) or exp experimental animal/ or animal experiment/ or animal model/ or exp rodent/ or editorial/ or letter/ or literature/ or case report/ or (rat or rats or mouse or mice or animal\* or letter\* or comment\* or abstracts).ti. or case report\*.ti,ab,kw. | 8542830 |
| 6 | (1 and 2 and 3) not 4 not 5 | 2805 |

Database(s): **PsycINFO**1806 to April Week 3 2016
Search Strategy:

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| --- | --- | --- |
| **#** | **Searches** | **Results** |
| 1 | \*esophagus/ or \*digestive system disorders/ or \*gastrointestinal disorders/ or ((gastroesophageal adj3 reflux\*) or (gastrooesophageal adj3 reflux\*) or (gastro esophageal adj3 reflux\*) or (gastro oesophageal adj3 reflux\*) or (GORD or GOR or GERD or GER) or (esophagitis or oesophagitis) or (gastric adj3 (acid or reflux\*)) or (reflux\* adj3 (oesophagitis or esophagitis)) or (erosive adj3 (oesophag\* or esophag\*))).ti,ab,id. | 1977 |
| 2 | exp pediatrics/ or childhood development/ or exp infant development/ or adolescent development/ or (child\* or infant\* or infancy or newborn\* or neonat\* or baby or babies or preschool or pre school or pubescen\* or teen\* or adolescen\* or puber\* or prepubert\* or juvenil\* or p?ediatric\* or youth\* or schoolchild\* or school age\* or schoolage\* or preschool or pre-school or elementary school or high school\* or highschool\* or kindergar\* or boy or boys or girl\* or minor\* or underag\* or under ag\* or kid or kids or toddler\*).ti,ab,id. or ("100" or "120" or "140" or "160" or "180" or "200").ag. | 1079577 |
| 3 | cohort analysis/ or prognosis/ or exp disease course/ or followup studies/ or exp longitudinal studies/ or "death and dying"/ or mortality rate/ or prediction/ or (incidenc\* or prognos\* or predict\* or course or cohort\* or surviv\* or mortalit\* or follow-up or followup or longitudinal or prospective\*).ti,ab,id. | 775682 |
| 4 | 1 and 2 and 3 | 176 |

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| --- | --- | --- | --- |
| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| **TITLE**  |  |
| Title  | 1 | Identify the report as a systematic review, meta-analysis, or both.  | 1 |
| **ABSTRACT**  |  |
| Structured summary  | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.  | 2 |
| **INTRODUCTION**  |  |
| Rationale  | 3 | Describe the rationale for the review in the context of what is already known.  | 4, 5 |
| Objectives  | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | 5 |
| **METHODS**  |  |
| Protocol and registration  | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.  | NA |
| Eligibility criteria  | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | 6 |
| Information sources  | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | 5 |
| Search  | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.  | 21, 22 |
| Study selection  | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).  | 6, 23 |
| Data collection process  | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | 6, 7 |
| Data items  | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.  | 6, 7 |
| Risk of bias in individual studies  | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | 6, 7 |
| Summary measures  | 13 | State the principal summary measures (e.g., risk ratio, difference in means).  | 7, 8 |
| Synthesis of results  | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.  | 7, 8 |

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|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| Risk of bias across studies  | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).  | 6, 7 |
| Additional analyses  | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.  | 7, 8 |
| **RESULTS**  |  |
| Study selection  | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  | 8, 23 |
| Study characteristics  | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.  | 8, 9, 24-26 |
| Risk of bias within studies  | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | 9, 27 |
| Results of individual studies  | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.  | 10-12, 28 - 33 |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | NA |
| Risk of bias across studies  | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | 9, 27 |
| Additional analysis  | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | NA |
| **DISCUSSION**  |  |
| Summary of evidence  | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).  | 14-17 |
| Limitations  | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).  | 16 |
| Conclusions  | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | 16, 17 |
| **FUNDING**  |  |
| Funding  | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.  | NA |

*From:*  Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

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  **Supplemental File 3 - Prisma 2009 Flow Diagram**

## Screening

## Included

## Eligibility

## Identification

Full-text articles assessed for eligibility
(n = 22)

Full-text articles excluded, with reasons
(n = 18)

Conference abstract n=1

Not in children n=3

No GERD n=7

No prospective study n=5

Not about prognosis n=2

Studies included in qualitative synthesis
(n = 4)

Studies included in quantitative synthesis (meta-analysis)
(not performed)

Records identified through database searching
(n = 5365)

Additional records identified through other sources
(n = 0)

Records after duplicates removed
(n = 3950)

Records screened
(n = 3950)

Records excluded
(n = 3928)

*From:*  Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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