BMJ Open

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|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-043860 |
| Article Type: | Original research |
| Date Submitted by the Author: | 15-Aug-2020 |
| Complete List of Authors: | Zheng, Zhoude; Peking Union Medical College Hospital, Department of Pulmonary and Critical Care Medicine<br>Luo, Yunyun; Peking Union Medical College Hospital, Department of Endocrinology<br>Gao, Jinming; Peking Union Medical College Hospital, Department of Pulmonary and Critical Care Medicine |
| Keywords: | Asthma < THORACIC MEDICINE, Oesophageal disease < GASTROENTEROLOGY, THERAPEUTICS |
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# Randomized trials of proton pump inhibitors for gastroesophageal reflux disease in patients with asthma: systematic review and meta-analysis

Zhoude Zheng, MD[1], Yunyun Luo, MD[2], Jinming Gao, MD PhD[1*]

[1]Department of Pulmonary and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China;
[2]Department of Endocrinology, Peking Union Medical College Hospital, Key Laboratory of Endocrinology of National Health Commission, Beijing, China

*Corresponding author: Jinming Gao, MD,PhD,
Peking Union Medical College Hospital (Dongdan campus), No.1 Shuaifuyuan Wangfujing Dongcheng District, Beijing, China.
E-mail: gjinming@yahoo.com Phone: +86 1860-1077-280

Key Words: Asthma; gastroesophageal reflux disease; proton pump inhibitors; meta-analysis

Word Count
Abstract: 245 Main Text: 3016

## ABSTRACT

**Objective** Asthma and gastroesophageal reflux disease (GERD) commonly co-exist. The effect of proton pump inhibitors (PPIs) treatment in asthma patients with GERD remains controversial. Thus, this study aimed to assess whether PPIs improved morning peak expiratory flow (mPEF) in asthma patients with GERD.

**Data Sources** PubMed, MEDLINE, EMBASE, Web of Science, Cochrane Library and ClinicalTrials.gov; hand searching of reference lists; contacted with authors if necessary.

**Study Selection** All eligible trials were randomized clinical trials comparing PPIs with placebo in patients with asthma accompanying with GERD.

**Results** Fourteen randomized clinical trials (2182 participants) were included. Overall, PPIs versus placebo did not affect mPEF in patients with asthma having GERD (weighted mean difference 8.68 L/min, 95% confidence interval [-2.35, 19.37], P=0.11). Trial sequential analysis (TSA) further confirmed this finding (TSA adjusted 95% CI [-1.03, 22.25]). Subgroups analyses based on the percentage of patients with symptomatic GERD ≥95%, treatment duration >12 weeks also found no statistically significant benefit on mPEF. Similarly, analyses of secondary outcomes (evening PEF, forced expiratory volume in 1 second, asthma symptoms score, asthma quality of life score and episodes of asthma exacerbation) did not show significant difference between PPIs and placebo.

**Conclusion** In this meta-analysis, PPIs therapy did not show a statistically significant improvement on mPEF in patients with asthma having GERD, neither in subgroup with symptomatic GERD nor in subgroup with treatment duration >12 weeks. This analysis does not support a recommendation for PPIs therapy as empirical treatment in asthma patients with GERD.

**Trial Registration:** PROSPERO CRD42020177330

## Strengths and limitations of this study

- This study is the first review evaluating the efficacy of proton pump inhibitors on several asthma outcomes in patients accompanying with gastroesophageal reflux disease, which was based on a comprehensive and systematic search with the largest number of participants to date.
- This study found for the first time that PPIs were ineffective on mPEF neither in asthma patients with symptomatic GERD nor in subgroup with treatment duration >12 weeks.
- Trial sequential analysis was applied in this meta-analysis, showing whether a clinical study could be terminated early when a P value is sufficiently small to show the expected effect.
- we could not extract the data from all the eligible trials with the outcomes of interest because of the unavailable reporting format. However, the overall sample size of these 3 trials was small and we do not think these studies would make a significant difference in our meta-analysis
- we could not perform a subgroup according to the severity of asthma or GERD as expected, because the severity reported inconsistently.

## INTRODUCTION

Asthma is a common chronic respiratory disease affecting 1–18% of the population in different countries and approximately 300 million people worldwide.[1 2] Gastroesophageal reflux disease (GERD) develops when the reflux of gastric contents causes irritating symptoms or complications, or both.[3] GERD was considered as a trigger factor for asthma. Symptoms and/or diagnosis of GERD presented in 30% to 90% of patients with asthma.[4-6] Association between asthma and GERD has been extensively described elsewhere. However, evidence of the causal link between asthma and GERD remains controversial. Some studies have shown that asthma may facilitate the development of GERD by the various mechanisms.[7 8]

PPIs were regarded as the cornerstone of antacid therapy and have been proved effective in empiric treatment of GERD.[9] Given that GERD may be a trigger for asthma, many randomized controlled trials (RCTs) were performed to identify the efficacy of different types of PPIs in the asthma patients with GERD.[10-23] However, the efficacy of PPIs for the patients with asthma accompanying with GERD remains inconsistent. Previous meta-analyses have pooled the results of PPIs on asthma outcomes in children and adults, but all of them included a small sample size.[24-26] The most recent systematic review examined the efficacy of PPIs treatment for the adults with asthma. However, the review did not study all the asthma outcomes, only involved mPEF in subgroup of asthmatic patients diagnosed with GERD, and failed to identify the clinical characteristics of this subgroup population.[27]

Thus, we did a systematic review and meta-analyses to compare the effects PPIs versus placebo on asthma outcomes in the patients with GERD. TSA was performed to quantify the meta-analysis monitoring boundaries and required information size (RIS) for primary outcome. Asthma outcomes included mPEF (primary outcome), evening peak expiratory flow (ePEF), forced expiratory volume in 1 second ($FEV_1$), asthma symptoms score, asthma quality of life, episodes of asthma exacerbation.

## METHOD AND ANALYSIS

The systematic review and meta-analyses were carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The protocol has been registered (CRD42020177330) with International Prospective Register of Systematic Reviews (PROSPERO).

### Eligibility criteria

Types of study

All randomized clinical trials of PPIs in the patients with asthma and GERD were included. The eligible randomized trials were required to report at least one clinical asthma outcome of interest.

Types of participants

Participants with asthma and GERD were eligible for inclusion. There were no restrictions regarding age, gender, and ethnicity. Asthma were diagnosed according to doctor's diagnosis, reported ongoing asthma-related symptoms, evidence of objective measures of lung function. GERD diagnosis based on doctors' diagnosis, reported clinical symptoms of GERD, and objective documentation.

Types of intervention and control

Trials comparing beneficial and harmful effects of PPIs with those of placebo were eligible. This review was restricted to studies with treatment duration of 4 weeks and above.[27] No restrictions were imposed on drug dosage and types of PPIs which contained omeprazole, lansoprazole, pantoprazole, esomeprazole, and rabeprazole. We excluded the trials that focused on the intervention with combination of PPIs and other antacids or gastrointestinal motility regulators.

Outcome measures

This review evaluated the following outcomes: mPEF, ePEF and $FEV_1$, which were commonly used as evidence of variable expiratory airflow obstruction.

Other outcomes included asthma symptoms score (validated questionnaires of all types), asthma quality of life (validated instruments of all types), episodes of asthma exacerbation and adverse events.

**Information sources and search**

A systematic search for evidence on the efficacy of PPIs on patients with asthma was performed through electronic databases, citation search based on reference lists and hand searching of main relevant journals. We did a search in PubMed, EMBASE, Web of Science, Cochrane Library and ClinicalTrials.gov dating from inception to 18th March, 2020. No restrictions were imposed on language, publication date, publication type, or publication status. The search terms and search strategies for all databases were described in the **supplement 1**.

**Study selection**

Two reviewers (ZZ and YL) independently screened titles and abstracts according to the eligibility criteria in an unblinded, standardized manner. Reviews, letters, editorials, case studies, non-human studies, study protocols, non-English-language abstract were excluded during this process. The assessments of eligible full-text articles were carried out independently by two reviewers (ZZ and YL). Disagreements between reviewers were resolved by consensus or referred to a third reviewer (JG) for resolution.

**Data extraction**

Two independent reviewers (ZZ and YL) extracted data from each eligible study by using a pre-designed extraction form. Discrepancies were resolved by consensus or by involvement of a third author (JG). Items of characteristics of included studies were described in **supplement 1**. We contacted the corresponding authors for outcomes data if required.

**Risk of bias in individual studies**

Two independent reviewers (ZZ and YL) evaluated risk of bias according to version 5.1.0 of Cochrane Handbook for Systematic Review of Interventions. An agreement was reached by discussion or by consultation with a third

review author (JG). The domains of evaluation for all the outcomes were selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Each potential source of bias was considered as either “high risk”, “low risk”, or “unclear risk”.

**Statistical analysis**

The weighted mean difference (WMD)/standardized mean difference (SMD) and 95% confidence intervals were calculated for continuous outcomes. The relative risk with 95% confidence intervals was calculated for dichotomous outcomes. Predefined subgroup analysis was undertaken in accordance with patients aged 18 years and older or patients younger than 18 years, the percentage of subjects with symptomatic GERD ≥95%, treatment duration (≤12 weeks VS >12 weeks) and types of PPIs (omeprazole, pantoprazole, lansoprazole, esomeprazole). Given the anticipated variability among patient characteristic and study design, a random effects model with 95% confidence intervals was used in the forest plots (RevMan version 5.3). Statistical heterogeneity was quantified using $I^2$ statistic, with $I^2$ cut-off value of 25%, 50%, and 75% to quantify low, moderate, and high thresholds, respectively. We conducted sensitivity analysis and Egger’s test to identify data stability and publication bias, respectively (StataSE 12.0). TSA (version of 0.9.5.10 Beta) was performed in mPEF and ePEF to quantify meta-analysis monitoring boundaries and RIS using parameters of mean difference of mPEF=20 L/min, estimate variance from the meta-analysis of PEF data, α at 0.05, power of 80%, and $I^2$ value of 0%.

**Patient and Public Involvement**

There was no patient or public involvement in this study.

## RESULTS

**Study selection and characteristics**

The search strategy yielded 2005 abstracts, of which 49 abstracts were

retrieved and under full-articles assessment for eligible articles. Of these trials, fourteen randomized controlled trials were included, six of which were cross-over studies,[10-12 14 15 20] and eight were of a parallel design.[13 16-19 21-23] The flow diagram for study inclusion is described in **Figure 1**. **Table 1** and **Supplement Table 1** summarizes the characteristics of the included studies (2182 participants) and the characteristics of the subjects, respectively. Of the 14 eligible trials, twelve included subjects aged ≥18 years, while only two aimed at patients aged <18 years (ranged from 6 to 17 years old).[17 23] Subjects were included with mild to severe asthma. The severity of GERD was reported inconsistently among the trials. Symptoms of heartburn, regurgitation and dysphagia were the common complications of GERD reported in most studies. The percentage of the subjects with symptomatic GERD was greater than 95% in 8 studies, of which 6 studies reported 100%.[10 11 14 17 20 22]

**Risk of bias within studies**

Each study was assessed in accordance with the Cochrane risk of bias tool (**Figure 2**).[28] Double-blinding method was adopted in all studies except one trial which used a single-blinding fashion.[20] Three trials were supported by pharmaceutical companies.[16 18 22]

**Outcomes**

Fourteen included studies investigated PPIs therapy on patients with asthma and GERD (2182 patients). Asthma outcomes were reported inconsistently among studies, leading to limitation of meta-analysis (**Table 2**). All studies reported one or more outcomes of lung function.

**Primary outcome**

Morning PEF

Three of eleven studies found a significant improvement on mPEF.[14 18 20] Eight studies containing nine groups were included in meta-analysis (1886 subjects). Among the nine groups, eight showed improvement in asthma symptoms,[10 12 13 16 18-20 22] but only one group did not cross the neutral

(zero) line.[19] The overall analysis found no statistically significant benefit on mPEF with PPIs treatment (8.68 L/min, 95% CI [-2.35, 19.37], P=0.11) (**Figure 3 A**). Heterogeneity was absent ($I^2$=0%; P=0.73). TSA showed a heterogeneity adjusted RIS of 1240 patients without the cumulative Z curve crossing boundaries for benefit or harm (TSA adjusted 95% CI [-1.03, 22.25]), suggesting that PPIs may not show benefit on mPEF of the patients with asthma and GERD (**Figure 4 A**). No publication bias reported in mPEF, and the sensitivity analysis confirmed the robustness of these findings (**Supplement 2**).

A subgroup was performed according to the percentage of subjects with symptomatic GERD ≥95%. Of eight eligible studies, five reported available data for meta-analysis.[10 12 16 20 22] No statistically significant effect was found for mPEF in this subgroup (7.07 L/min, 95% CI [-6.56, 20.69], P=0.31) (**Figure 3 B**). TSA showed that only 1158 (79%) of the heterogeneity adjusted RIS of 1470 patients were calculated. However, the cumulative Z curve crossed the boundaries for futility (TSA adjusted 95% CI [-5.94, 25.58]) (**Figure 4 B**). Next, we conducted subgroups analysis based on duration of PPIs treatment (duration ≤12 weeks VS >12 weeks). No statistically significant benefit was demonstrated in both subgroups (duration ≤12 weeks: 23.06 L/min, 95% CI [-3.40, 49.51], P=0.09, P=0.43; duration >12 weeks: 5.87 L/min, 95% CI [-5.83, 17.56], P=0.33) (**Figure 3 C**).Then we conducted TSA in the subgroup with duration >12 weeks. TSA did not alter the efficacy on mPEF with a PPIs treatment duration >12 weeks (TSA adjusted 95% CI [-4.99, 20.50]) (**Figure 4 C**). Also, three subgroups meta-analyses based on types of PPIs did not showed statistically significant treatment benefit (omeprazole: 4.65 L/min, 95% CI [-35.43, 44.72], P=0.27; pantoprazole: 29.18 L/min, 95% CI [-23.21, 81.56], P=0.31; esomeprazole: 5.91 L/min, 95% CI [-7.02, 18.84], P=0.37) on mPEF (**Figure 3 D**).

**Secondary outcomes**

Evening PEF

Ten trials reported ePEF of the subjects with asthma and GERD, of which two trials demonstrated statistically significant improvement on ePEF.[12 18] Of these 10 trials, 6 studies provided information and were included in the meta-analyses.[10 12 16 18-20] Meta-analysis did not show statistically significant effect on ePEF (5.58 L/min; 95% CI [-8.19, 19.36]; P=0.43) (**Figure 5 A**). TSA showed that the cumulative Z curve crossed boundaries for futility, suggesting no statistically significant improvement on ePEF with PPIs therapy (TSA adjusted 95% CI [- 6.87, 25.35]). No publication bias reported in ePEF, and the sensitivity analysis showed solid results (**Supplement 3a**).

No statistically significant benefit was showed on ePEF by subgroups analyses of the studies in accordance with the percentage of subjects with symptomatic GERD ≥95%, length of PPIs treatment and types of PPIs (**Supplement 3b**).

Forced expiratory volume in 1 second

Three studies provided information of $FEV_1$ % predicted,[12 18 19] and only two provided available data of $FEV_1$ (L),[13 16] which were included in analyses, respectively. At the analysis of $FEV_1$ % predicted, no therapy effect was found on the patients with PPIs use (-1.25%, 95% CI [-4.9, 3.00], P=0.56) (**Figure 5 B1)**. Heterogeneity was substantial ($I^2$=61%; P=0.05). The analysis of the two studies may not demonstrated a benefit on the $FEV_1$ (L) in the patients with PPIs therapy (-0.09 L, 95% CI [-0.28, 0.10], P=0.36) (**Figure 5 B2**). No publication reported in FEV1 % predicted, the sensitivity analysis showed robust results (**Supplement 4**).

Asthma symptoms score

Six studies reported information of asthma symptoms score and were included in meta-analysis.[10 13 16 17 19 20] Five of six trials included the patients aged older than 18 years. The subgroup of adults showed no statistically significant effect on asthma symptoms score with PPIs treatment (SMD -0.30, 95% CI [-0.61, 0.01], P=0.06, heterogeneity $I^2$=32%, P=0.21). However, the analysis found a small statistically significant improvement on

asthma symptoms score (SMD -0.26, 95% CI [-0.52, -0.01], P=0.04), when we pooled the studies in adults and those in children. Heterogeneity was low ($I^2$=19%, P=0.29) (**Figure 5 C**). No publication reported in asthma symptoms score, and the sensitivity analysis showed that the results were robust (**Supplement 5**).

Asthma quality of life

Four eligible studies were included for meta-analysis.[16 18 19 23] The result showed no overall effect on the asthma quality of life (SMD 0.01, 95% CI [-0.44, 0.47], P=0.96). Heterogeneity was substantial ($I^2$=89%, P<0.00001) (**Figure 5 D**). No publication bias was reported in this outcome (P=0.588), but sensitivity analysis showed the results were unstable (**supplement 6**). Therefore, the pooled result for asthma quality of life had limited meaning.

Episodes of asthma exacerbation

Only two studies provided information of episodes of asthma exacerbation and showed an improvement in this variance.[16 22] However, no effect was showed in meta-analysis (relative risk 0.55, 95% CI [0.21, 1.43], P=0.22). Heterogeneity was substantial ($I^2$=81%, P<0.02) (**Figure 5 E**).

## DISCUSSION

For primary outcome mPEF, we assessed 8 studies including 9 independent comparisons (1886 participants) and found no statistically significant improvement with PPIs treatment in patients with asthma and GERD compared to placebo. Subgroups analyses according to duration >12 weeks and the percentage of subjects with symptomatic GERD ≥95%, did not demonstrated statistically significant benefit with PPIs therapy. Also, no statistically significant improvement was observed on the secondary outcomes including ePEF, $FEV_1$, asthma symptoms, quality of life and asthma exacerbation.

To enlarge sample size, our analysis not only included trials with asthma subjects having GERD diagnosis for entry criterion, but also those reported

GERD subjects in subgroups analyses.[18 20] To the best of our knowledge, this analysis included the largest number of participants to date describing the effect of PPIs treatment in patients with asthma accompanying with GERD. The previous meta-analysis aiming to examine the efficacy of PPIs in the adult patients with asthma, reported a subgroup analysis based on GERD diagnosis for entry criterion with 7 trials (1004 patients).[27] In contrast to our study, a small statistically significant improvement was reported for mPEF in this subgroup, therefore, this analysis might overestimate the benefits on mPEF and exaggerate the effect of positive improvement, because of incomplete and inadequate population inclusion. However, in line with our results, this previous review did not show benefit on in patients with asthma with PPIs treatment on ePEF, $FEV_1$, asthma symptoms score and asthma quality of life.

A study reported that the minimal patient perceivable improvement differences for PEF was 18.79 L/min.[29] The minimal difference in PEF ranging from 15 to 20 L/min were summarized in a review.[30] Our analysis found that the pooled mean difference for mPEF and ePEF were 7.30 and 5.58 L/min respectively, which were far smaller than the minimal effective line, probably showing a lack of evidence to believe the efficacy of PPIs. In alignment with our study, previous meta-analysis published by Cochrane Collaboration found no statistically significant improvement on mPEF and ePEF.[25] Also, a recent large three-arms RCT was consistent with our study.[22]

Several trials have reported that PPIs played no role in asthma patients with asymptomatic GERD, whether in children or adults.[21 23] Similarly, in our subgroup meta-analysis, no statistically significant benefit appeared for mPEF in asthma patients with symptomatic GERD. This result was in keeping with a large trial including all asthma participants with symptomatic GERD.[22] Our subgroup analysis for mPEF based on duration >12 weeks was conducted, suggesting that no improvement appeared with PPIs therapy. In

agreement with our result, two large trials did not find improvement for mPEF with PPIs treatment for 24 or 26 weeks.[16 22]

Mechanistically, GERD may trigger asthma via directly damage to the respiratory tree leading to bronchoconstriction by micro-aspiration of gastric or duodenal (or both) contents.[31 32] Previous studies have reported that bile acids and pepsin were found graft failure in lung transplant patients, indicating that acid materials may not be the only one of many irritants in the aspirate during gastroesophageal reflux.[33 34]

PPIs treatment significantly improved asthma symptoms and lung function in patients with exercise-triggered asthma, with asthma and nocturnal respiratory symptoms, or taking LABAs.[18 35] It appeared that benefits of PPIs may be restricted to patients with certain types or status of asthma. Further studies are warranted to examine the pathophysiological mechanism to determine the causality between asthma and GERD. Notably, if the improvement for asthma conditions were delayed or required more time to present, then the overall effect may be underestimated. Thus, further RCTs should be conducted with a treatment period for more than 6 months. Previous RCTs combined omeprazole and domperidone therapy in patients with asthma and GERD, showing that combined therapy improved asthma symptoms and lung function with treatment period of 12 or 16 weeks.[36 37] Therefore, the efficacy of combined therapy should be further explored. Furthermore, we hopefully expect the effect of genotype-tailored PPIs in patients with asthma and co-morbid GERD.[38]

There are several limitations in the present study. Firstly, we could not extract the data from all the 11 eligible trials reporting mPEF, because of the unavailable reported form (mean difference only,[14] medians and quartiles[15]) or unavailable data in subgroup.[21] However, the overall sample size of these 3 trials was small and we do not think these studies would make a significant difference in our meta-analysis. Secondly, we could not perform a subgroup according to the severity of asthma or GERD as

expected, because the severity reported inconsistently and we could not sort out the disease status of each trial. Thirdly, only two RCTs in children were eligible in the present study, making it difficult to evaluate the effect for PPIs on all outcomes in children.[17 23] However, both trials reported no improvement for PPIs in all the asthma outcomes, which were in line with the overall effect in adults in our analysis.

**CONCLUSION**

Compared to placebo, PPIs therapy for asthma patients with GERD did not show statistically significant improvement in mPEF. This futility did not alter in asthma patients neither with symptomatic GERD nor with PPIs treatment for more than 12 weeks. This analysis does not support a recommendation for the empirical use of PPIs therapy in asthma patients having GERD.

**Acknowledgements:**

The authors would like to thank Dr. Xiaoling Li for her suggestions on grammar and vocabularies of this manuscript. We would also like to thank Dr. Xiaorui Lyu (Department of Endocrinology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College) for his advice on data analysis data extraction. This work was supported by the National Natural Science Foundation of China (Grant No. 81970025).

**Author contributions**

ZZ led the meta-analysis was involved at every stage, including protocol development, screening, data extraction, quality assessment, data analysis and manuscript drafting. YL was involved in screening, data extraction, quality assessment, interpretation of results and manuscript revisions. JG supervised this review and was involved in protocol preparation, consensus on disagreement in data extraction, quality assessment, data analysis, interpretation of results, manuscript drafting and revisions.

**Conflicts of interests**

None declared.

**Funding**

This work was supported by the National Natural Science Foundation of China (81970025).

**Patient consent for publication**

Not required.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Data sharing statement**

No additional data are available.



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**List of Figures**

**Table 1** Summary of participants characteristics of included studies

| Trials | Mean (SD or range) Age (Years) | Male, n (%) | Severity of asthma | Severity of GERD | Complications of GERD | Symptomatic GERD (%) | Association between asthma and GERD reported |
|---|---|---|---|---|---|---|---|
| Ford 1994 | 63 (50-80) | 5 (50%) | Mean PEFR before and after terbutaline use (SD), 1/minute: 253 (83) and 308 (±94) | Number per grade of esophagitis: Grade I (n=1), Grade II (n=2), Grade III(n=4); Barrett's esophagus (n=2 | Heartburn, regurgitation, lack of proportion | 100% | No |
| Meier 1994 | 49 (34-63) | 9 (60%) | Not stated; inclusion criteria: reversibility of $FEV_1$ and/ or PEF after bronchodilator use: >15% | Number per grade of esophageal inflammation: Grade I (n=1), Grade II (n= 4), Grade III (n= 8), Grade IV (n= 2); hiatal hernia n=10; Barrett's esophagus and peptic stricture n=10 | Not specified | 100% | Yes |
| Teichtahl 1996 | 46 (12) | 12 960% ) | Not stated, inclusion criteria: reversibility of $FEV_1$ >15%; diurnal variation of PEF: >20% | GERD symptoms in all | Not specified | 95% | No |
| Boeree 1998 | 51 (10) | 17 (47.2%) | Mean $FEV_1$ %, pred (SD): Int 66(20); cont 75(23); mPEF mean (SD): Omeprazole group 329 (91); placebo group 321 (109) | Increased gastroesophageal reflux reported in all | Dysphagia Int n=2/1/0, Cont n=3/0/0; heartburn Int n=9/0/0, Cont n=9/3/0; regurgitation Int n=3/0/0, Cont n=4/3/0 | 50% | No |
| Levin 1998 | 57 (35–72) | 6 (67%) | Mean $FEV_1$ (range): 1.9 (1.0–2.9); mean PEFR (range), L/min: mPEF 376 (283–488), ePEF 381 (286–468). | 24-h pH monitoring, mean % time with pH < 4 (range): total: 24.4 (4.7–64.0), supine: 17.6 (0–39.8), upright: 23.8 (5.6–74.4) | Not specified | 100% | No |
| Kiljander 1999 | 49 (21–75) | 18(35%) | Mean PEF (range) L/min, 455 (250 to 700); $FEV_1$% of predicted (range), 81 (31 to 114) | Median % time pH < 4 (75–25% quartiles) : total 9.0 (14.7–5.0), upright 10.1 (15.1–6.9), supine: 4.0 (15.7–0.8) | Not specified | 65% | No |
| Littner 2005 | 47 (12) | 66 (31.9%) | Moderate-to-severe persistent asthma | Mean severity score (SD): Overall reflux symptoms: Int 1.66 (0.69), Cont 1.70 (0.65) ¶ | Patients with symptoms (%): heartburn Int 97%, Cont 95%; regurgitation Int 80%, Cont 80%; dysphagia: Int 32%, Cont 47% | Int 96.1±8.0%, Cont 97.3±5.2% | No |
| Størdal 2005 | 10.2 (9.2), 11.3 (11.0) | 29 (76.3%) | GINA classification of asthma severity (step 1/2/3/4): Int 4/8/7/0, Cont 3/6/10/0 . | Reflux index, mean (%, SD): Int 8.8 (4.0), Cont 9.7 (5.1); reflux index≥ 10% (n): Int n=5, Cont n=6 | Not specified | 100% | No |
| Kiljander 2006 GERD+/NOC+ (Kiljander-1) | 46.3 | 80 (36.5%) | $FEV_1$, % pred: Int 67.3%, Cont 66.2%; Morning PEF, % pred: Int 73.0%, Cont 73.0% | Abnormal 24-h esophageal pH in all | Mean number heartburn symptoms/day: (nighttime) Int 0.42, Cont 0.44; (daytime) Int 0.68, Cont 0.71 | Not stated | Yes |
| Kiljander 2006 GERD+/NOC- (Kiljander-2) | 44.3 | 94 (26.9%) | $FEV_1$, % pred: Int 65.5%, Cont 67.4%; mPEF, % pred: Int 68.7%, Cont 69.2%. | Abnormal 24-h esophageal pH in all | Mean number heartburn symptoms/day: (nighttime) Int 0.46, Cont 0.47; (daytime) Int 0.68, Cont 0.62 | | |
| dos Santos 2007 | Int 40 (12), Cont 45 (12) | 9 (22.0%) | Mean $FEV_1$% predicted (SD): Int 61.6 (19), Cont 60.4 (19); mean diurnal PEF (SD): Int 317 (13), Cont 264 (86) | Mean GERD symptoms score (SD): Int 12.9 (9), Cont 11.4 (7) | Not specified | 80% | No |
| Susanto 2008 | Int 42.69 (11.11), Cont 37.88 (11.01) | 9 (28.1%) | Moderate persistent asthma; mean $FEV_1$% prediction (SD): Int 72.9 (6.7), Cont 71.2 (7.7); mean PEFR, L/min (SD): Int 258.8 (33.2), Cont 269.5 (76.4) | One or more typical GERD symptoms in all. patients with histopathological esophagitis (%): 87.5% | Heartburn: Int 68%. Cont 87%; atypical chest pain: Int 81.3%, Cont 75%, regurgitation: Int 100%, Cont 100%, dysphagia: Int 12.5%, Cont 25%, water brash: Int 37.5%, Cont 37.5% | 100% | No |
| Mastronarde 2009 | (>18) | Not stated | Persistent and poorly controlled asthma | PH monitoring positive in all | Not specified | 0% | No |
| Kiljander 2010 | 45 (19-70) | 233 (24.3%) | Moderate-to-severe asthma | Moderate severity | Heartburn, acid regurgitation Dyspepsia | 100% | No |
| Holbrook 2012 | (6-17) | Not stated | Poorly controlled asthma | Abnormal 24-h esophageal pH in all | Not specified | 0% | No |

Abbreviations: $FEV_1$, forced expiratory volume in 1 second; mPEF, morning peak expiratory flow; PEFR peak expiratory flow; pred, predicted; PUD, peptic ulcer disease; GERD, gastroesophageal reflux disease; GINA: Global Initiative for Asthma; Int, intervention; Cont, control; PPI, proton pump inhibitor; NOC, nocturnal respiratory symptoms; SD, standard deviation

¶ An investigator-assessed scale was used, as follows: 0, none; 1, mild; 2, moderate; and 3, severe.

**Table 2** Summary of results of PPIs treatment on asthma outcomes

| Trials | mPEF, L/min | ePEF, L/min | $FEV_1$, L | $FEV_1$%, Pred | Asthma symptom score | AQLQ | Episodes of asthma exacerbation |
|---|---|---|---|---|---|---|---|
| Ford 1994 | - | - | NA | NA | - | NA | NA |
| Meier 1994 | NA | NA | - | NA | - | NA | NA |
| Teichtahl 1996 | - | + | NA | - | NA | NA | NA |
| Boeree 1998 | - | - | - | NA | - | NA | NA |
| Levin 1998 | + | - | - | NA | NA | + | NA |
| Kiljander 1999 | - | - | +* | NA | + | NA | NA |
| Littner 2005 | - | - | - | - | - | + | + |
| Størdal 2005 | NA | NA | - | NA | - | - | NA |
| GERD+/NOC-, Kiljander-1 2006 | - | - | NA | - | - | - | NA |
| GERD+/NOC+, Kiljander-2 2006 | + | + | NA | - | - | - | NA |
| dos Santos 2007 | - | - | NA | - | - | + | NA |
| Susanto 2008 | + | - | NA | NA | + | NA | NA |
| Mastronarde 2009 | - | NA | - | NA | - | - | NA |
| Kiljander 2010 | - | - | + | | - | + | + |
| Holbrook 2012 | NA | NA | - | NA | NA | - | NA |

Abbreviations: $FEV_1$, forced expiratory volume in 1 second; pred, predicted; mPEF, morning peak expiratory flow; AQLQ, Asthma Quality of Life Questionnaire; NA, not available; +, significant therapy effect; -, not significant therapy effect.

*, Decline during omeprazole use.

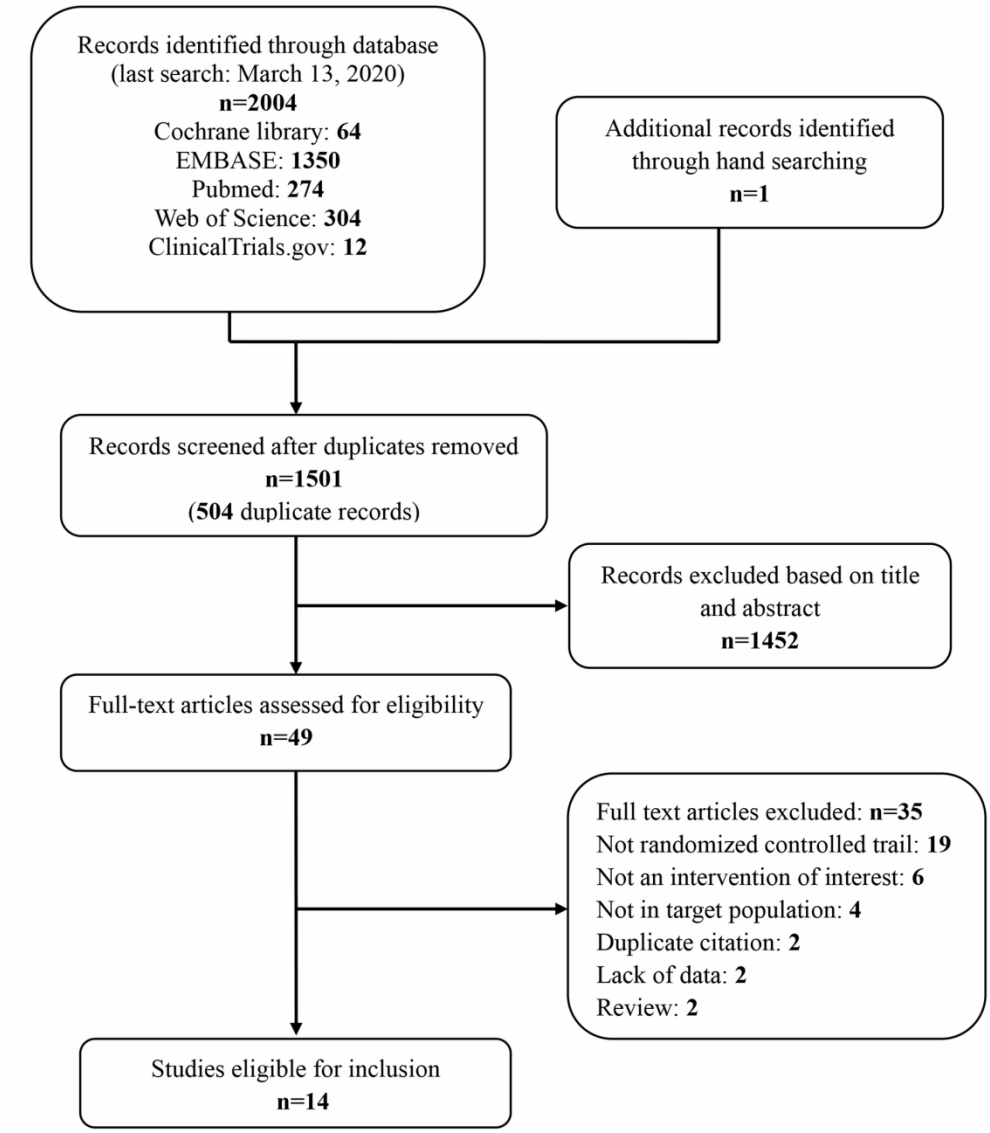


Figure 1 Flow diagram of identification of eligible studies for inclusion.

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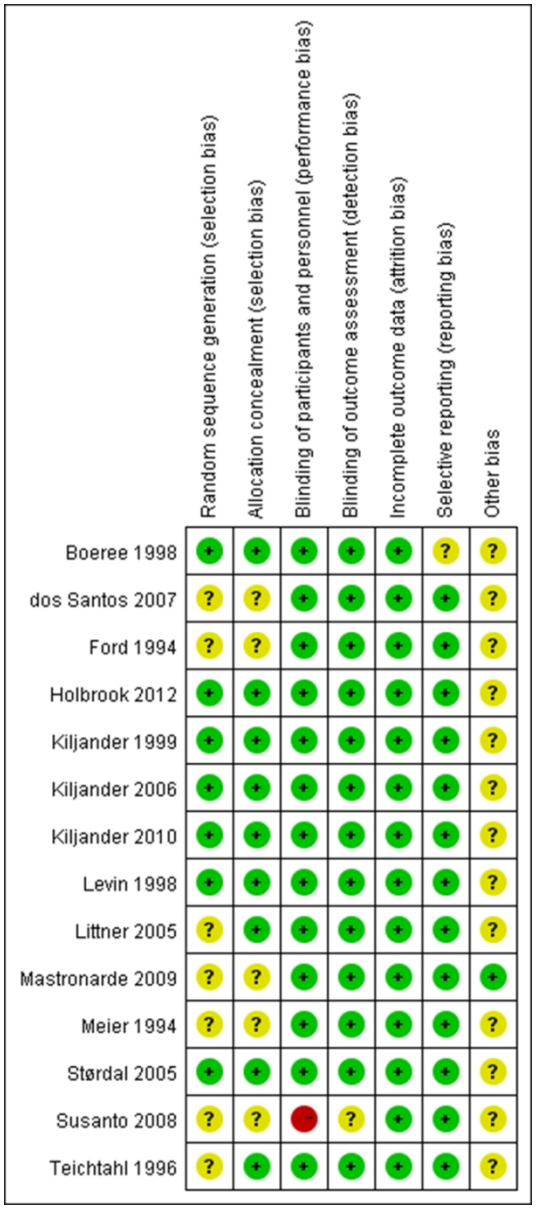


Figure 2 Risk of bias summary displaying review authors' judgements about each risk of bias item for each included study.

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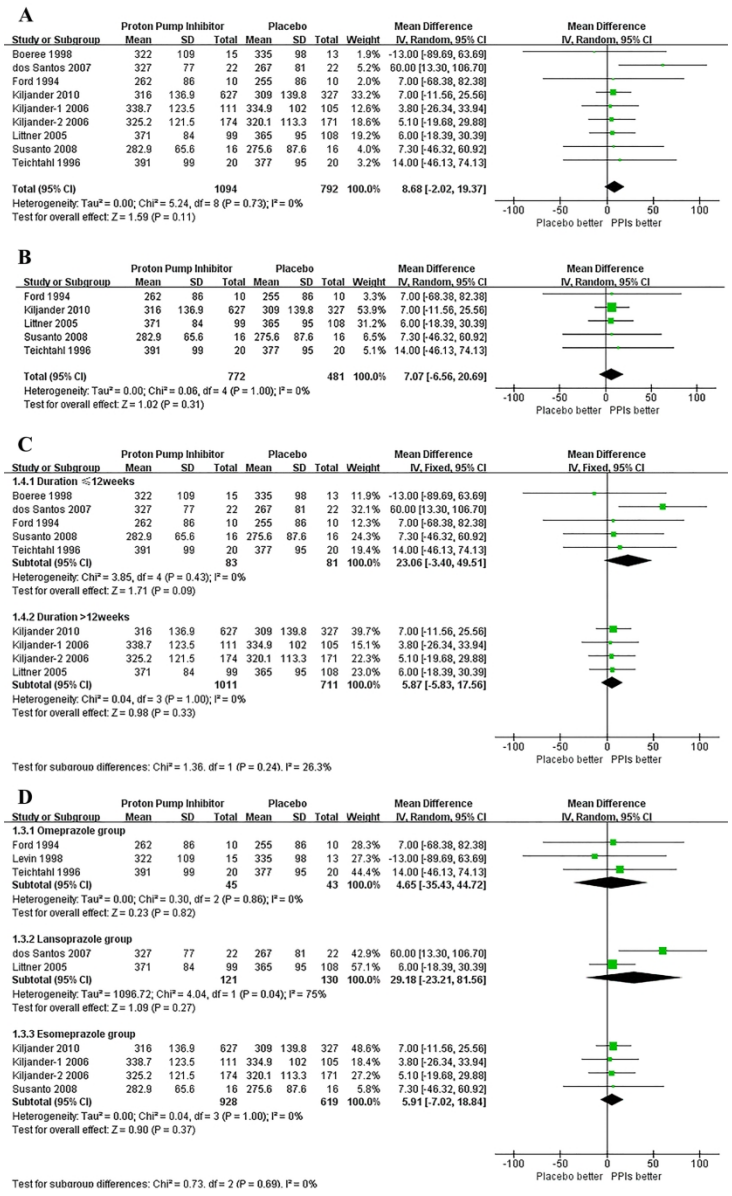


Figure 3 A, Forest plot for morning peak expiratory flow. B, Forest plot for morning peak expiratory flow in subgroup of the percentage of subjects with symptomatic GERD ≥95%. C, Forest plot for morning peak expiratory flow in subgroups of treatment duration ≤12 weeks and >12 weeks. D, Forest plot for morning peak expiratory flow in subgroups of different types of proton pump inhibitors.

72x119mm (600 x 600 DPI)

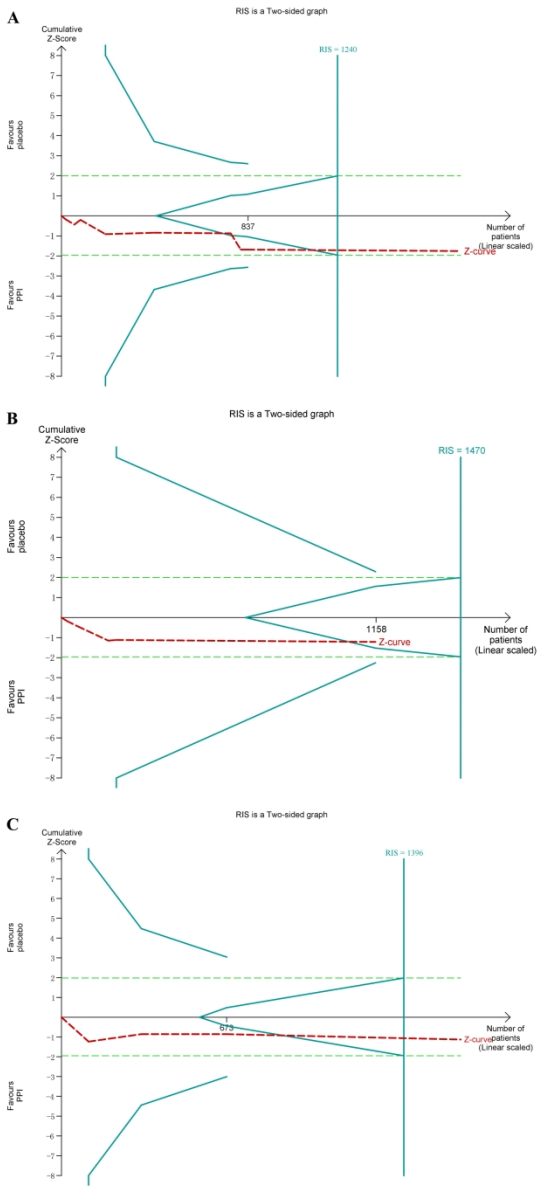


Figure 4 A, Trial sequential analysis of morning peak expiratory flow. B, Trial sequential analysis of morning peak expiratory flow in subgroup of the percentage of subjects with symptomatic GERD ≥95%. C, Trial sequential analysis of morning peak expiratory flow in subgroup of of treatment duration >12 weeks.

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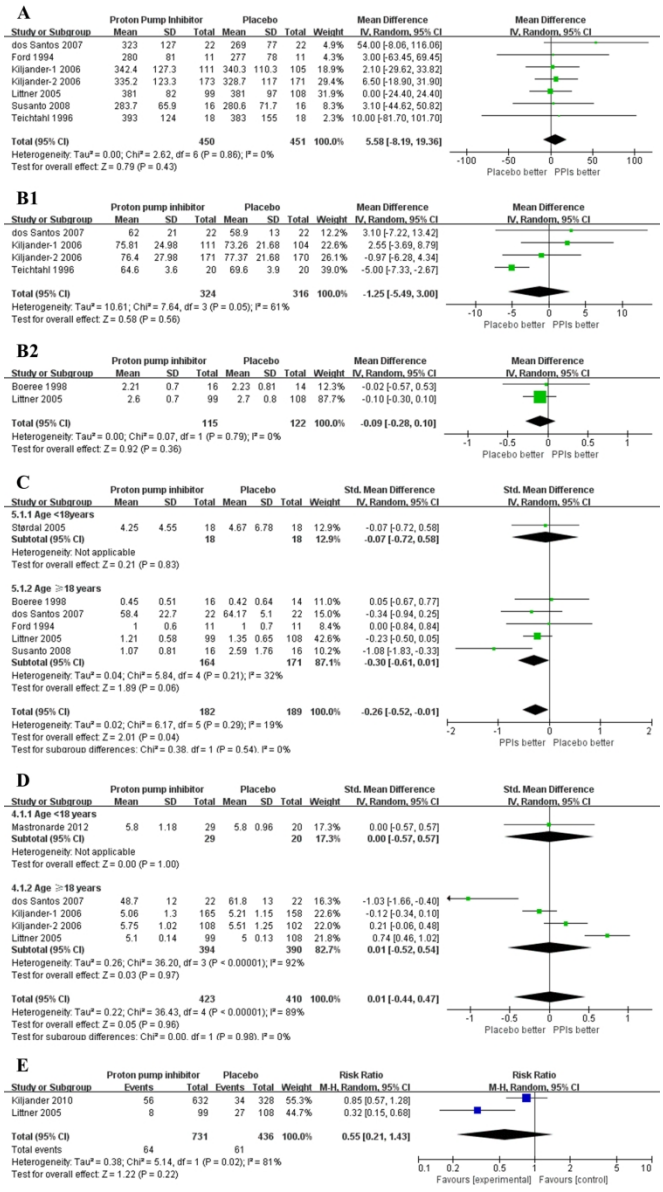



Figure 5 A, Forest plot for evening peak expiratory flow. B1, Forest plot for FEV1 % predicted. B2, Forest plot for FEV1 (L). C, Forest plot for asthma symptoms score. D, Forest plot for asthma quality of life score. E, Forest plot for episodes of asthma exacerbation.

72x133mm (600 x 600 DPI)

**Supplement Table 1** Summary of the characteristics of included studies

| Trials | Location | Study design | Medication/dose and usage | Concurrent treatment | Duration (weeks) | Number of Randomized/Completed patients | | Inclusion criteria | | Concurrent disease | Major exclusions |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Intervention group | Control group | Asthma diagnosis | GERD Diagnosis | | |
| Ford 1994 | UK | Crossover | Omeprazole 20 mg, qd | ICS 80%, ipratropium 10% | 4 | Total: 11/10 | | Doctor's diagnosis; reversibility PEFR after bronchodilator use: ≥15%; nocturnal asthma attack | Abnormal pH in 24-h pH monitoring; upper gastrointestinal endoscopy; history of esophagitis | Not stated | Not specified |
| Meier 1994 | America | Crossover | Omeprazole 20 mg, bid | Asthma medications (lack of type), theophylline 11/15 | 6 | Total: 15/15 | | ATS; reversibility of $FEV_1$ and/ or PEF after bronchodilator use: >15% | Abnormal pH in 24-h pH monitoring; manometry; esophagogastroduodenoscopy; acid-perfusion (Bernstein) test | Not stated | ≤18 years old. pregnancy, female unwilling to use birth contraception; unable to give informed consent |
| Teichtahl 1996 | Australia | Crossover | Omeprazole 40 mg, qd | Other asthma medications; Iβ2A | 4 | Total: 25/20 | | Doctor's diagnosis; positive HIT; diurnal variation of PEFR ≥20%; reversibility of $FEV_1$ and/ or PEF after bronchodilator use: >15% | Abnormal pH in 24-h pH monitoring; endoscopy | Not stated | Other significant respiratory disease; respiratory tract infection; significant systemic, esophageal stricture |
| Boeree 1998 | The Netherlands | Parallel | Omeprazole 40 mg, bid | ICS 0.4 mg/day used in all | 12 | 18/16 | 18/14 | Doctor's diagnosis; $FEV_1$ >1.25 L, PC20 <2 mg/mL | Abnormal pH in 24-h pH monitoring, increased GER was defined as >4% of 24 h registration, or >3% during the supine position | COPD | Upper and/or lower respiratory tract infection, other concomitant lung diseases |
| Levin 1998 | America | Crossover | Omeprazole 20 mg, qd | Inhaled β-agonists used in all | 8 | total: 11/9 | | Doctor's diagnosis; ≥15% reversibility in $FEV_1$ after bronchodilator treatment; asthma medication used daily | Symptoms of heartburn or regurgitation at least once weekly without therapy; manometry, ambulatory 24-h esophageal pH monitoring | Not stated | COPD, URTI, prior gastroesophageal surgery, acute PUD, use of omeprazole or URTI within previous 30 days |
| Kiljander 1999 | Finland | Crossover | Omeprazole 40 mg, qd | $Iβ_2A$ 91%; ICS 89% | 8 | total: 57/52 | | Doctor's diagnosis; ATS | 24-h pH monitoring and manometry | Not stated | Not specified |
| Littner 2005 | multi-center, North America | Parallel | Lansoprazole 30 mg, bid | ICS, stable doses of asthma medications for at least 4 wks | 24 | 99/85 | 108/88 | Doctor's diagnosis; $FEV_1$ pred > 50% and < 85%; ≥12% improvement in $FEV_1$ (in liters) after the inhalation of 180 ug of albuterol; five or more nocturnal asthma awakenings and receiving stable doses of asthma medications within previous 4 wks | Investigator judgement based on symptomatic acid reflux and acid-suppressive therapy; 24-h esophageal pH monitoring | Not stated | Smoking; receiving ipratropium bromide, immunotherapy; URTI; uncontrolled medical condition; receiving PPI within 14 days |
| Størdal 2005 | Norway | Parallel | Omeprazole 20 mg, qd | ICS: Int n=17, Cont n=17; long acting bronchodilators: Int 10, Cont 12 | 12 | 19/18 | 19/18 | Doctor's diagnosis; at least two episodes of asthma symptoms requiring medication within previous six months | 24-h pH monitoring; A reflux index ≥5.0 was considered abnormal | Not stated | Previously known or treated GERD |
| Kilja nder 2006 GERD+/ NOC+ (Kiljander-1) | Europe, North America, South America | Parallel | Esomeprazole 40 mg, qd | ICS: 98.6%; LABAs: 49.8% | 16 | 112/105 | 107/105 | $FEV_1$% pred: 50 to 80%, ≥12% (and ≥0.20 L) reversibility; PEF pred <80%; symptom of nighttime awakening with related respiratory symptoms; or PEF | Heartburn ≥2 times/wk; acid regurgitation ≥once /wk within previous 3 month. erosive esophagitis or Barrett's esophagus (without dysplasia) documented in the previous | Not stated | Smoking; esophageal or gastric surgery; glucocorticosteroids <30 days; erosive esophagitis ≤16 wks and PPI use <14 days before enrollment; |
| GERD+/ NOC- | | Parallel | Esomeprazole 40 mg, bid | ICS: 97.7%; LABAs: 34% | 16 | 174/174 | 176/171 | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| (Kiljander-2) | | | | | | | overnight variability ≥15% | 12 months; abnormal 24-h esophageal pH | | recurrent moderate or severe GERD symptoms |
| dos Santos-2007 | Brazil | Parallel | Pantoprazole 40 mg, qd | long-acting β2 -agonists (%): Int 45%, Cont 64%; oral corticoids: Int 9%, Cont 18% | 12 | total: 44 (Int n=22, Cont n=22)/35 | Asthmatic clinical history and symptoms for at least two months; airflow obstruction ($FEV_1$/FVC) < 90% of predicted; the methacholine bronchoprovocation test (+), obstruction reversibility: $FEV_1$ >200 mL and 7% of predicted | 24-h esophageal pH monitoring; manometry | Not stated | Smoking; receiving PPI and H-2 receptor blocker; systemic arterial hypertension |
| Susanto-2008 | Indonesia | Crossover | Esomeprazole 40 mg, qd | inhaled budesonide 400 µg bid, salbutamol 100 mg/puff | 8 | 18/16 | 18/16 | GINA 2002 | Endoscopy and or esophageal histopathologic examination; typical GERD symptoms | Not stated | Not specified |
| Mastronarde-2009 | Multicenter, North America | Parallel | Esomeprazole 40 mg, bid | ICS in all | 24 | 61 /61 | 62 /62 | Doctor's diagnosis; positive methacholine challenge test; 12% increase in $FEV_1$ after bronchodilator treatment | 24-h pH monitoring, mean % time with pH < 4 (range): total >5.8%, upright >8.2%, supine <3.5% | Not stated | Smoking; $FEV_1$% pred <50%; surgery; acid-suppression treatment |
| Kiljander-2010 | Multicenter, Europe, North America, South America | Parallel | Esomeprazole 40 mg, qd/bid | ICS and LABA in all | 26 | 40 mg, qd: 313/273; 40 mg, bid: 320/272 | 328/283 | Doctor's diagnosis; ATS | The validated Reflux Disease Questionnaire, esophageal 24-h pH monitoring | Not stated | Alarm symptoms presented, smoking, esophageal or gastric surgery, Barrett esophagus |
| Holbrook 2012 | America | Parallel | Lansoprazole, children <30 kg: 15 mg/d; children ≥30 kg: 30 mg/d | ICS in all | 24 | 29 /29 | 20 /20 | Doctor's diagnosis; ≥12% in $FEV_1$ after bronchodilator treatment; PC20 ≤16 mg/mL; positive exercise bronchoprovocation test | Ambulatory esophageal pH monitoring: time of pH <4 in 6- to 11-year-old for ≤6%, in 12- to 17-year-old for ≤4% | Not stated | Receiving PPI or other reflux medications; anti-reflux surgery or trachea-esophageal fistula repair; $FEV_1$% pred <60% |

Abbreviations: LABA, long-acting $\beta_2$ -agonists, $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; PC20, provocative concentration of methacholine bromide causing a ≥20% fall in forced expiratory volume in 1 second; I$\beta_2$A, inhaled $\beta_2$ -agonists, ICS, inhaled corticosteroid; mPEF, morning peak expiratory flow; PEFR morning peak expiratory flow; pred, predicted; PUD, peptic ulcer disease; URTI, upper respiratory tract infection; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; GINA: Global Initiative for Asthma; ATS: American Thoracic Society; Int, intervention; Cont, control; wks, weeks; qd, once daily; bid, twice daily; PPI, proton pump inhibitor, NOC, nocturnal respiratory symptoms; SD, standard deviation; HIT histamine bronchoprovocation test; NA, not available

# Appendix

## Supplement 1

### Information sources and search

The search terms of asthma included: “asthma”, “asthma bronchiale”, “asthma pulmonale”, “asthmatic”, “asthmatic subject”, “bronchial asthma”, “bronchus asthma”, “childhood asthma”, “chronic asthma”, “lung allergy” and “asthmatics”.

The search terms of gastroesophageal reflux disease contained: “gastroesophageal reflux”, “gerd”, “gastroesophageal reflux disease”, “gord”, “cardioesophageal reflux”, “esophageal reflux”, “esophageal regurgitation”, “esophagogastric reflux”, “esophagus reflux”, “gastric regurgitation”, “gastro esophageal reflux”, “gastro oesophageal reflux”, “gastroesophageal reflex”, “gastroesophageal regurgitation”, “gastroesophagus reflux”, “gastrooesophageal reflex”, “gastrooesophageal reflux”, “gastrooesophageal reflux disease”, “gastrooesophageal regurgitation”, “oesophageal reflux”, “oesophageal regurgitation”, “oesophagogastric reflux”, and “oesophagus reflux”

The search terms of contained: “proton pump inhibitor”, “proton pump inhibitors”, “PPI” “pantoprazole”, “omeprazole”, “esomeprazole”, “lansoprazole”, and “rabeprazole”.

(search strategies for all databases)

Medline via Ovid, 2020,3,18

| # | Term | Result |
|---|---|---|
| #1 | "randomized controlled trial".pt. | |
| #2 | (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab. | |
| #3 | (retraction of publication or retracted publication).pt. | |
| #4 | or/1-3 | |

| | | |
|---|---|---|
| #5 | (animals not humans).sh. | |
| #6 | ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt. | |
| #7 | (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt. | |
| #8 | 4 not (5 or 6 or 7) | |
| #9 | (asthma$ or bronchial asthma$).ti,ab. | |
| #10 | exp asthma$/ | |
| #11 | exp "gastroesphageal reflux"/ or gastroesophageal reflux.ti,ab,kf. or exp Gastric Acid Reflux/ or exp Gastric Acid Reflux Disease/ or exp gastro-Esophageal Reflux/ or exp Gastro Esophageal Reflux/ or exp Gastroesophageal Reflux Disease/ or exp GERD/ or exp Esophageal Reflux/ or exp Gastro-oesophageal Reflux/ or exp Gastro oesophageal Reflux/ | |
| #12 | (Gastric Acid Reflux or Gastric Acid Reflux Disease or Gastro-Esophageal Refluxor Gastro Esophageal Reflux or Gastroesophageal Reflux Disease or GERD or Esophageal Reflux or Gastro-oesophageal Reflux or Gastro oesophageal Reflux).ti,ab,kf. | |
| #13 | 9 or 10 | |
| #14 | 11 or 12 | |
| #15 | 13 and 14 | |

| | | |
|---|---|---|
| #16 | exp proton pump inhibitor$/ | |
| #17 | exp omeprazole/ or exp lansoprazole/ or exp pantoprazole/ or exp rabeprazole/ or exp esomeprazole/ or exp ilaprazole/ | |
| #18 | (omeprazole or lansoprazole or pantoprazole or rabeprazole or esomeprazole or ilaprazole or proton pump inhibitor$).ti,ab,kf. | |
| #19 | 16 and 17 and 18 | |
| #20 | 8 and 15 and 19 | 12 |

Pubmed 2020,3,18

| # | Term | Result |
|---|---|---|
| #1 | Search "Asthma"[Mesh] | 126238 |
| #2 | Search "asthma*"[Title/Abstract] | 146574 |
| #3 | Search “Bronchial Asthma”[Title/Abstract] | 18297 |
| #4 | Search (((((("asthma bronchiale"[Title/Abstract]) OR "asthma pulmonale"[Title/Abstract]) OR "asthmatic"[Title/Abstract]) OR "asthmatics"[Title/Abstract]) OR "bronchus asthma"[Title/Abstract]) OR "childhood asthma"[Title/Abstract]) OR " chronic asthma"[Title/Abstract]) OR "lung allergy"[Title/Abstract] | 42241 |
| #5 | #1 OR #2 OR #3 OR #4 | 175686 |
| #6 | Search "Gastroesophageal Reflux"[Mesh] | 26315 |
| #7 | Search ((((((((((((((((((("gastroesophageal reflux"[Title/Abstract]) OR "gerd"[Title/Abstract]) OR | 26101 |

| | | |
|---|---|---|
| | "gastroesophageal reflux disease"[Title/Abstract]) OR "gord"[Title/Abstract]) OR "cardioesophageal reflux"[Title/Abstract]) OR "esophageal reflux"[Title/Abstract]) OR "esophageal regurgitation"[Title/Abstract]) OR "esophagogastric reflux"[Title/Abstract]) OR "esophagus reflux"[Title/Abstract]) OR "gastric regurgitation"[Title/Abstract]) OR "gastro esophageal reflux"[Title/Abstract]) OR "gastro oesophageal reflux"[Title/Abstract]) OR "gastroesophageal reflex"[Title/Abstract]) OR "gastroesophageal regurgitation"[Title/Abstract]) OR "gastroesophagus reflux"[Title/Abstract]) OR "gastrooesophageal reflex"[Title/Abstract]) OR "gastrooesophageal reflux"[Title/Abstract]) OR "gastrooesophageal reflux disease"[Title/Abstract]) OR "gastrooesophageal regurgitation"[Title/Abstract]) OR "oesophageal reflux"[Title/Abstract]) OR "oesophageal regurgitation"[Title/Abstract]) OR "oesophagogastric reflux"[Title/Abstract]) OR "oesophagus reflux"[Title/Abstract] | |
| #8 | #6 OR #7 | 35248 |
| #9 | #5 AND #8 | 2083 |
| #10 | Search "Proton Pump Inhibitors"[Mesh] | 10998 |
| #11 | Search "proton pump inhibitors"[Title/Abstract] | 8793 |
| #12 | Search (((((("omeprazole"[Title/Abstract]) OR | 12476 |

| | | |
|---|---|---|
| | "lansoprazole"[Title/Abstract]) OR "pantoprazole"[Title/Abstract]) OR "rabeprazole"[Title/Abstract]) OR "esomeprazole"[Title/Abstract]) OR "ilaprazole"[Title/Abstract] | |
| #13 | #10 OR #11 OR #12 | 23677 |
| #14 | #9 AND #10 | 274 |

Embase 3,18,2020

| # | Term | Result |
|---|---|---|
| #1 | ('asthma'/exp OR 'asthma' OR 'asthma bronchiale' OR 'asthma pulmonale' OR 'asthma, bronchial' OR 'asthmatic' OR 'asthmatic subject' OR 'bronchial asthma' OR 'bronchus asthma' OR 'childhood asthma' OR 'chronic asthma' OR 'lung allergy') AND ('gastroesophageal reflux'/exp OR 'gerd (gastroesophageal reflux disease)' OR 'gerd (gastrooesophageal reflux disease)' OR 'gord (gastrooesophageal reflux disease)' OR 'cardioesophageal reflux' OR 'cardiooesophageal reflux' OR 'esophageal reflux' OR 'esophageal regurgitation' OR 'esophagogastric reflux' OR 'esophagus reflux' OR 'gastric regurgitation' OR 'gastro esophageal reflux' OR 'gastro oesophageal reflux' OR 'gastroesophageal reflex' OR 'gastroesophageal reflux' OR 'gastroesophageal reflux disease' OR 'gastroesophageal regurgitation' OR 'gastroesophagus reflux' OR 'gastrooesophageal reflex' OR 'gastrooesophageal reflux' OR | 858 |

| | | |
|---|---|---|
| | 'gastrooesophageal reflux disease' OR 'gastrooesophageal regurgitation' OR 'oesophageal reflux' OR 'oesophageal regurgitation' OR 'oesophagogastric reflux' OR 'oesophagus reflux' OR 'reflux, gastroesophageal' OR 'reflux, gastrooesophageal' OR 'regurgitation, gastric' OR 'regurgitation, gastroesophageal' OR 'regurgitation, gastrooesophageal') AND ('proton pump inhibitors':ti,ab OR 'lansoprazole'/exp OR '2 [ [[3 methyl 4 (2, 2, 2 trifluoroethoxy) 2 pyridyl] methyl] sulfinyl] 1h benzimidazole' OR 'a 65006' OR 'a65006' OR 'abt 006' OR 'abt006' OR 'ag 1749' OR 'ag1749' OR 'agopton' OR 'bamalite' OR 'banilux' OR 'betalans' OR 'compraz' OR 'dakar (drug)' OR 'daxar' OR 'dostab' OR 'duomate' OR 'ilsatec' OR 'inhipraz' OR 'keval' OR 'lancid' OR 'lancopen' OR 'langaton' OR 'lanpra' OR 'lanpraz' OR 'lanprol' OR 'lanproton' OR 'lansazol' OR 'lansobene' OR 'lansol' OR 'lansone' OR 'lansop' OR 'lansopep' OR 'lansoprazol' OR 'lansoprazole' OR 'lansox' OR 'lansozole' OR 'lanster' OR 'lanston' OR 'lanvell' OR 'lanximed' OR 'lanzo' OR 'lanzol-30' OR 'lanzopral' OR 'lanzoprazole' OR 'lanzor' OR 'lanzul' OR 'lapraz' OR 'laprazol' OR 'laproton' OR 'lasgan' OR 'limpidex' OR 'lopral' OR 'monolitum' OR 'ogast' OR 'ogasto' OR 'ogastoro' OR 'ogastro' OR 'opiren' OR 'pampe' OR 'praton' OR 'prevacid' OR 'prevacid 24 hr' OR 'prevacid fastab' OR 'prevacid iv' OR 'prevacid solutab' OR 'prezal' OR 'prolanz' OR 'prosogan' OR 'pysolan' OR 'sopralan-30' OR 'suprecid' OR 'takepron' OR | |

| | | |
|---|---|---|
| | 'takepron od' OR 'tanzolan' OR 'ulpax' OR 'zoton' OR 'zoton fastab' OR 'omeprazole'/exp OR '5 methoxy 2 [ [(4 methoxy 3, 5 dimethyl 2 pyridyl) methyl] sulfinyl] benzimidazole' OR 'aleprozil' OR 'antra' OR 'antra mups' OR 'arapride' OR 'audazol' OR 'baromezole' OR 'desec' OR 'dolintol' OR 'domer' OR 'dudencer' OR 'duogas' OR 'emeproton' OR 'epirazole' OR 'ezipol' OR 'gasec' OR 'gasec gastrocaps' OR 'gastec' OR 'gastop' OR 'gastrimut' OR 'gastrolac' OR 'gastroloc' OR 'glaveral' OR 'h 168 68' OR 'h 168-68' OR 'h-etom' OR 'h168 68' OR 'h168-68' OR 'hovizol' OR 'hyposec' OR 'inhibitron' OR 'inhipump' OR 'logastric' OR 'lomac' OR 'lopraz' OR 'losamel' OR 'losec' OR 'losec mups' OR 'losecosan' OR 'ludea' OR 'madiprazole' OR 'maxor' OR 'medoprazole' OR 'medral' OR 'meiceral' OR 'mepral' OR 'mepzol' OR 'mezzopram' OR 'miol' OR 'miracid' OR 'mopral' OR 'mopralpro' OR 'nocid' OR 'ocid' OR 'ogal' OR 'olexin' OR 'omedar' OR 'omelon' OR 'omep uno' OR 'omepral' OR 'omeprazen' OR 'omeprazol' OR 'omeprazole' OR 'omeprazole magnesium' OR 'omeprazole sodium' OR 'omeprazon' OR 'omepril' OR 'omeraz' OR 'omesec' OR 'omestad' OR 'omezin' OR 'omezol' OR 'omezolan' OR 'omezole' OR 'omezzol' OR 'omisec' OR 'omizac' OR 'omolin' OR 'ompranyt' OR 'omprazole' OR 'onexal' OR 'oprax' OR 'ozoken' OR 'parizac' OR 'penrazole' OR 'pepticum' OR 'peptidin' OR 'peptilcer' OR 'peptizole' OR 'pra-sec' OR 'prazidec' OR 'prazole' | |

| | | |
|---|---|---|
| | OR 'prilosec' OR 'prilosec otc' OR 'prisolec' OR 'probitor' OR 'proceptin' OR 'protoloc' OR 'ramezol' OR 'rapinex' OR 'reglacid' OR 'result (drug)' OR 'risek' OR 'romep' OR 'roweprazol' OR 'secrepina' OR 'severon' OR 'stomacer' OR 'stomec' OR 'stozole' OR 'suifac' OR 'ulceral' OR 'ulcozol' OR 'ulnor' OR 'ulsek' OR 'ulsen' OR 'ulzol' OR 'vulcasid' OR 'wonmp' OR 'xoprin' OR 'zatrol' OR 'zefxon' OR 'zenpro' OR 'zimor' OR 'zoltum' OR 'pantoprazole'/exp OR '5 difluoromethoxy 2 [ (3, 4 dimethoxy 2 pyridyl) methylsulfinyl] 1h benzimidazole' OR 'anagastra' OR 'branzol' OR 'by 1023' OR 'by1023' OR 'controloc' OR 'controloc control' OR 'eupantol' OR 'inipom' OR 'inipomp' OR 'pantecta' OR 'pantecta control' OR 'pantodac' OR 'pantodar' OR 'pantoloc' OR 'pantoloc control' OR 'pantop' OR 'pantoprazole' OR 'pantoprazole sodium' OR 'pantoprazole sodium sesquihydrate' OR 'pantozol' OR 'pantozol control' OR 'pepticus' OR 'protium' OR 'protonix' OR 'protonix iv' OR 'rifun' OR 'rifun 40' OR 'sk and f 96022' OR 'skf 96022' OR 'skf96022' OR 'somac' OR 'somac control' OR 'ulcepraz' OR 'ulcotenal' OR 'ziprol' OR 'zurcal' OR 'zurcale' OR 'zurcazol' OR 'rabeprazole'/exp OR '2 [ [4 (3 methoxypropoxy) 3 methyl 2 pyridyl] methylsulfinyl] benzimidazole' OR 'aciphex' OR 'aciphex sprinkle' OR 'dexrabeprazole' OR 'e 3810 (benzimidazole derivative)' OR 'e3810 (benzimidazole derivative)' OR 'ly 307640' OR 'ly307640' OR 'pariet' OR 'pariprazole' OR 'pariprazole sodium' OR 'rabec' | |

| | | |
|---|---|---|
| | OR 'rabeloc' OR 'rabeprazole' OR 'rabeprazole sodium' OR 'esomeprazole'/exp OR 'esomeprazol' OR 'esomeprazole' OR 'esomeprazole magnesium' OR 'esomeprazole potassium' OR 'esomeprazole sodium' OR 'esoprax' OR 'h 199 18' OR 'h 199-18' OR 'h 19918' OR 'h199 18' OR 'h199-18' OR 'h19918' OR 'inexium' OR 'nexium' OR 'nexium 24hr' OR 'nexium control' OR 'nexium iv' OR 'nexium-mups' OR 'perprazole' OR 'sompraz' OR 'ilaprazole'/exp OR '2 [ (4 methoxy 3 methyl 2 pyridyl) methylsulfinyl] 5 (1 pyrrolyl) 1h benzimidazole' OR 'ilaprazole' OR 'iy 81149' OR 'iy81149') | |
| #2 | 'asthma*':ab,ti OR 'asthma bronchiale':ab,ti OR 'asthma pulmonale':ab,ti OR 'asthmatic':ab,ti OR 'asthmatics':ab,ti OR 'asthmatic subject':ab,ti OR 'bronchial asthma':ab,ti OR 'bronchus asthma':ab,ti OR 'childhood asthma':ab,ti OR 'chronic asthma':ab,ti OR 'lung allergy':ab,ti | 230139 |
| #3 | 'asthma'/exp OR asthma | 321680 |
| #4 | #2 OR #3 | 324305 |
| #5 | 'gastroesophageal reflux'/exp OR 'gastroesophageal reflux' | 66642 |
| #6 | 'gastroesophageal reflux':ab,ti OR 'gerd':ab,ti OR 'gastroesophageal reflux disease':ab,ti OR 'gord':ab,ti OR 'cardioesophageal reflux':ab,ti OR 'esophageal reflux':ab,ti OR 'esophageal regurgitation':ab,ti OR 'esophagogastric reflux':ab,ti OR 'esophagus reflux':ab,ti OR 'gastric regurgitation':ab,ti OR 'gastro esophageal reflux':ab,ti | 41444 |

| | | |
|---|---|---|
| | OR 'gastro oesophageal reflux':ab,ti OR 'gastroesophageal reflex':ab,ti OR 'gastroesophageal regurgitation':ab,ti OR 'gastroesophagus reflux':ab,ti OR 'gastrooesophageal reflex':ab,ti OR 'gastrooesophageal reflux':ab,ti OR 'gastrooesophageal reflux disease':ab,ti OR 'gastrooesophageal regurgitation':ab,ti OR 'oesophageal reflux':ab,ti OR 'oesophageal regurgitation':ab,ti OR 'oesophagogastric reflux':ab,ti OR 'oesophagus reflux':ab,ti | |
| #7 | #5 OR #6 | 70399 |
| #8 | #4 AND #7 | 5602 |
| #9 | 'omeprazole'/exp OR 'proton pump inhibitor'/exp OR 'lansoprazole'/exp OR 'pantoprazole'/exp OR 'rabeprazole'/exp OR 'esomeprazole'/exp OR 'ilaprazole'/exp | 76773 |
| #10 | 'omeprazole':ab,ti OR 'proton pump inhibitor':ab,ti OR 'lansoprazole':ab,ti OR 'pantoprazole':ab,ti OR 'rabeprazole':ab,ti OR 'esomeprazole':ab,ti OR 'ilaprazole':ab,ti | 27726 |
| #11 | #9 OR #10 | 78726 |
| #12 | #8 AND #11 | 1328 |
| #13 | #1 OR #12 | 1350 |

Note：#1 Retrieval strategy was through “PICO” in Embase.

Web of science 18,3,2020

| # | Term | Result |
|---|---|---|
| #1 | TS=(“gastroesophageal reflux”) OR TS=(“gerd ‘:ab,ti OR ‘gastroesophageal reflux disease”) OR TS=(“gord ‘:ab,ti OR ‘cardioesophageal reflux”) OR TS=(“esophageal reflux”) OR TS=(“esophageal regurgitation”) OR TS=(“esophagogastric reflux”) OR TS=(“esophagus reflux”) OR TS=(“gastric regurgitation”) OR TS=(“gastro esophageal reflux”) OR TS=(“gastro oesophageal reflux”) OR TS=(“gastroesophageal reflex”) OR TS=(“gastroesophageal regurgitation”) OR TS=(“gastroesophagus reflux”) OR TS=(“gastrooesophageal reflex”) OR TS=(“gastrooesophageal reflux”) OR TS=(“gastrooesophageal reflux disease”) OR TS=(“gastrooesophageal regurgitation”) OR TS=(“oesophageal reflux”) OR TS=(“oesophageal regurgitation”) OR TS=(“oesophagogastric reflux”) OR TS=(“oesophagus reflux”) | |
| #2 | TS=(“asthma*”) OR TS=(“asthma bronchiale”) OR TS=(“asthma pulmonale”) OR TS=(“asthmatic”) OR TS=(“asthmatics”) OR TS=(“asthmatic subject”) OR TS=(“bronchial asthma”) OR TS=(“bronchus asthma”) OR TS=(“childhood asthma”) OR TS=(“chronic asthma”) OR TS=(“lung allergy”) | |
| #3 | #2 AND #1 | |
| #4 | TS=("omeprazole") OR TS=("proton pump inhibitor*") OR TS=("lansoprazole") OR TS=("pantoprazole") OR | |

| | | |
|---|---|---|
| | TS=("rabeprazole") OR TS=("esomeprazole") OR TS=("ilaprazole") | |
| #5 | #4 AND #3 | 304 |

Cochrane library 18,3,2020

| # | Term | Result |
|---|---|---|
| #1 | MeSH descriptor: [Asthma] explode all trees | |
| #2 | MeSH descriptor: [Gastroesophageal Reflux] explode all trees | |
| #3 | (“asthma” OR “asthma bronchiale” OR “asthma pulmonale” OR “asthmatic” OR “asthmatic subject” OR “bronchial asthma” OR “bronchus asthma” OR “childhood asthma” OR “chronic asthma” OR “lung allergy” OR “asthmatics”):ti,ab,kw | |
| #4 | (“gastroesophageal reflux” OR “gerd “ OR “gastroesophageal reflux disease” OR “gord “ OR “cardioesophageal reflux” OR “esophageal reflux” OR “esophageal regurgitation” OR “esophagogastric reflux” OR “esophagus reflux” OR “gastric regurgitation” OR “gastro esophageal reflux” OR “gastro oesophageal reflux” OR “gastroesophageal reflex” OR “gastroesophageal regurgitation” OR “gastroesophagus reflux” OR “gastrooesophageal reflex” OR “gastrooesophageal reflux” OR “gastrooesophageal reflux disease” OR “gastrooesophageal regurgitation” OR “oesophageal reflux” OR “oesophageal regurgitation” OR “oesophagogastric reflux” OR “oesophagus reflux”):ti,ab,kw | |

| | | |
|---|---|---|
| #5 | #1 OR #3 | |
| #6 | #2 OR #4 | |
| #7 | #5 AND #6 | |
| #8 | MeSH descriptor: [Proton Pump Inhibitors] explode all trees | |
| #9 | ("proton pump inhibitors"):ti,ab,kw | |
| #10 | MeSH descriptor: [Esomeprazole] explode all trees | |
| #11 | ("esomeprazole"):ti,ab,kw | |
| #12 | ("omeprazole" OR "lansoprazole" OR "pantoprazole" OR "rabeprazole" OR "esomeprazole" OR "ilaprazole"):ti,ab,kw | |
| #13 | MeSH descriptor: [Lansoprazole] explode all trees | |
| #14 | MeSH descriptor: [Pantoprazole] explode all trees | |
| #15 | MeSH descriptor: [Rabeprazole] explode all trees | |
| #16 | #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 | |
| #17 | #7 AND #16 | 63 |

Clinical trail (US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov)18,3,2020

Retrieval strategy:

"Proton Pump Inhibitors" OR "omeprazole" OR "lansoprazole" OR "pantoprazole" OR "rabeprazole" OR "esomeprazole" OR "ilaprazole" | Completed Studies | "asthma" and "gastroesophageal reflux"

Applied Filters: Completed

Results: 12

**Data extraction**

Data of the included studies characteristics were collected if available. (a) Items of characteristics of included studies contained study location, study design, medication type/dose/usage, concurrent treatment, treatment duration, randomized and completed sample size, diagnostic inclusion criteria of asthma and GERD, concurrent diseases, major exclusions; (b) items of subject characteristics included age, male proportion, severity of asthma and GERD, complications of GERD, proportion of symptomatic GERD, and whether the association between asthma and GERD were reported; (c) items of effect of each outcome mentioned above included mean, standard deviation (SD), 95% confidence interval, median, interquartile range, and/or range.

If trials reported more than one eligible comparison group (for example, intervention group-1 VS control group-1 and intervention group-2 VS control group-2), these were considered independent studies and these data were extracted respectively if available. Three-arm trials (for example, two intervention groups VS control group) were combined appropriately into one PPI group and one placebo group.

**Supplement 2**

No publication bias reported in mPEF (P=0.342). Both sensitivity analysis and egger's test further supported the overall results were stable.

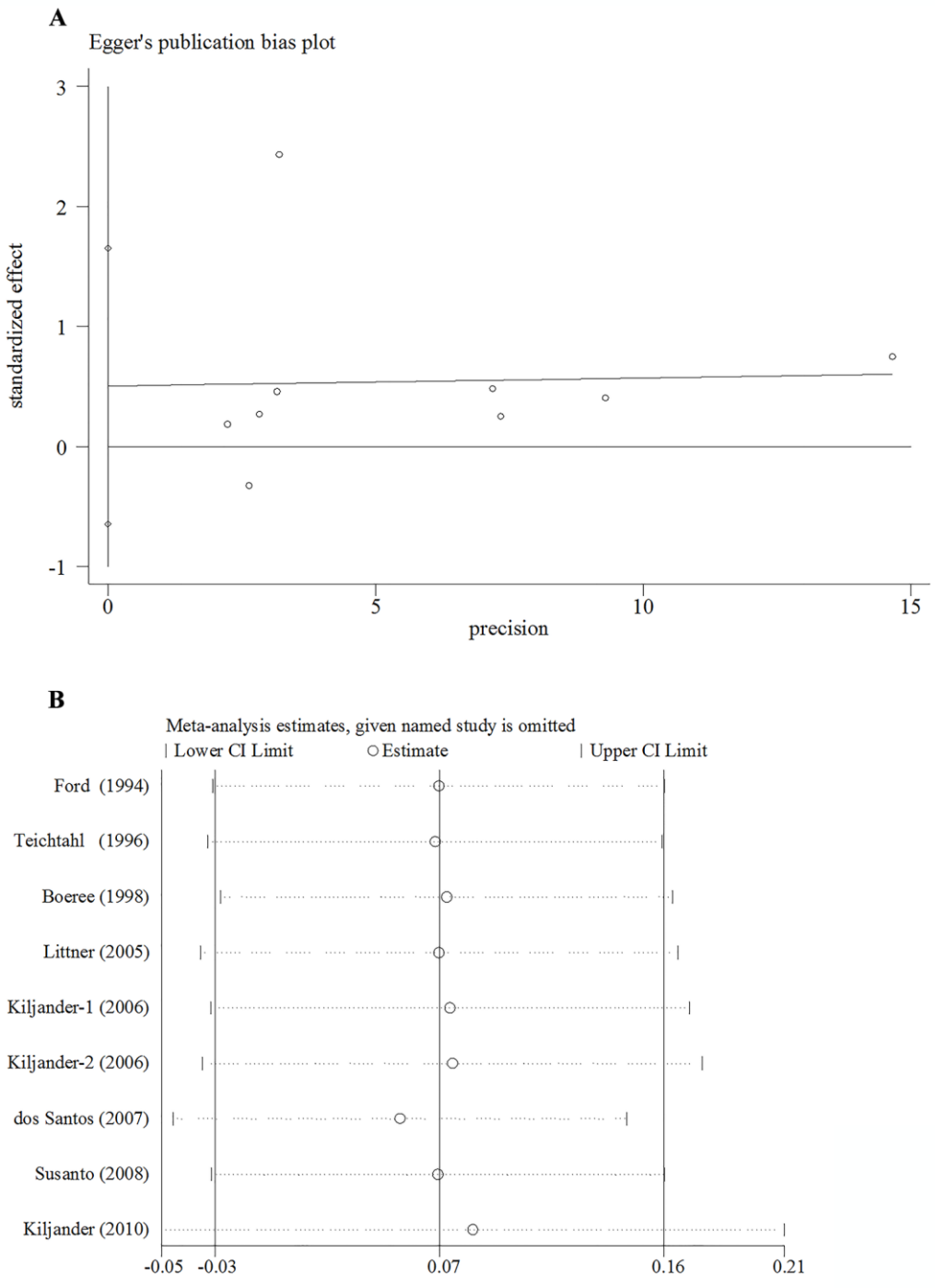



**Fig S2 A,** Egger's publication bias plot for mPEF (P=0.336). **B,** Sensitivity analysis for mPEF.

**Supplement 3**

**a.** No publication bias reported in ePEF (P=0.342). Both sensitivity analysis and egger's test further supported the overall results were stable.

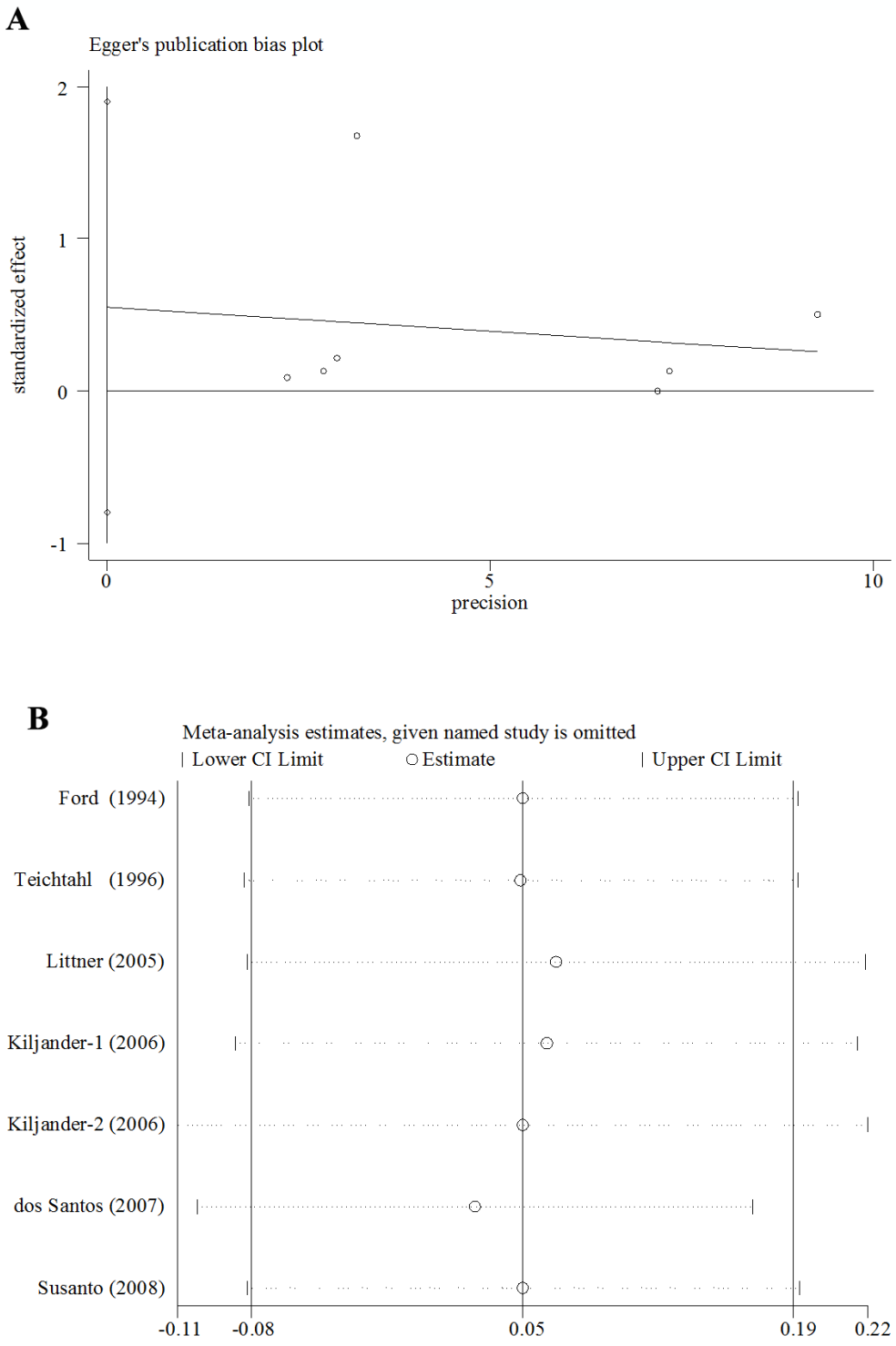
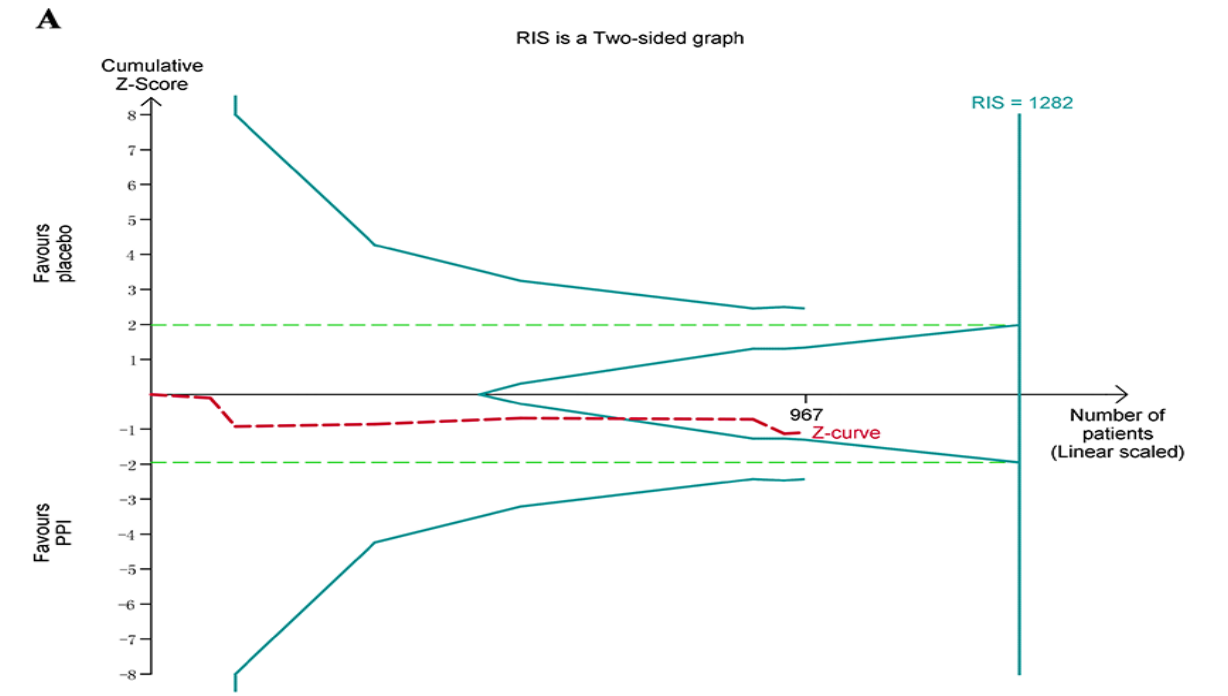



**Figure S3a A,** Egger's publication bias plot for ePEF (P=0.342). **B,** Sensitivity analysis for ePEF.

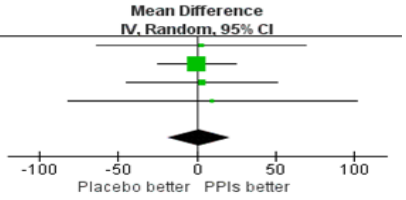
**b.**




**B**

| Study or Subgroup | Proton Pump Inhibitor Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Ford 1994 | 280 | 81 | 11 | 277 | 78 | 11 | 9.2% | 3.00 [-63.45, 69.45] |
| Littner 2005 | 381 | 82 | 99 | 381 | 97 | 108 | 68.2% | 0.00 [-24.40, 24.40] |
| Susanto 2008 | 283.7 | 65.9 | 16 | 280.6 | 71.7 | 16 | 17.8% | 3.10 [-44.62, 50.82] |
| Teichtahl 1996 | 393 | 124 | 18 | 383 | 155 | 18 | 4.8% | 10.00 [-81.70, 101.70] |
| **Total (95% CI)** | | | **144** | | | **153** | **100.0%** | **1.31 [-18.84, 21.46]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 3 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)




**C**

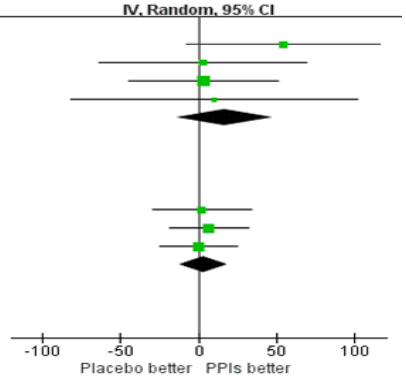
| Study or Subgroup | Proton Pump Inhibitor Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.4.1 Duration ≤12 weeks** | | | | | | | | |
| dos Santos 2007 | 323 | 127 | 22 | 269 | 77 | 22 | 24.9% | 54.00 [-8.06, 116.06] |
| Ford 1994 | 280 | 81 | 11 | 277 | 78 | 11 | 21.7% | 3.00 [-63.45, 69.45] |
| Susanto 2008 | 283.7 | 65.9 | 16 | 280.6 | 71.7 | 16 | 42.1% | 3.10 [-44.62, 50.82] |
| Teichtahl 1996 | 393 | 124 | 18 | 383 | 155 | 18 | 11.4% | 10.00 [-81.70, 101.70] |
| **Subtotal (95% CI)** | | | **67** | | | **67** | **100.0%** | **16.52 [-14.43, 47.47]** |

Heterogeneity: Tau² = 0.00; Chi² = 1.88, df = 3 (P = 0.60); I² = 0%
Test for overall effect: Z = 1.05 (P = 0.30)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **2.4.2 Duration >12weeks** | | | | | | | | |
| Kiljander-1 2006 | 342.4 | 127.3 | 111 | 340.3 | 110.3 | 105 | 23.5% | 2.10 [-29.62, 33.82] |
| Kiljander-2 2006 | 335.2 | 123.3 | 173 | 328.7 | 117 | 171 | 36.7% | 6.50 [-18.90, 31.90] |
| Littner 2005 | 381 | 82 | 99 | 381 | 97 | 108 | 39.8% | 0.00 [-24.40, 24.40] |
| **Subtotal (95% CI)** | | | **383** | | | **384** | **100.0%** | **2.88 [-12.51, 18.27]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 2 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)

Test for subgroup differences: Chi² = 0.60, df = 1 (P = 0.44), I² = 0%




**D**

| Study or Subgroup | Proton Pump Inhibitor Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.3.1 Omeprazole group** | | | | | | | | |
| Ford 1994 | 280 | 81 | 11 | 277 | 78 | 11 | 65.6% | 3.00 [-63.45, 69.45] |
| Teichtahl 1996 | 393 | 124 | 18 | 383 | 155 | 18 | 34.4% | 10.00 [-81.70, 101.70] |
| **Subtotal (95% CI)** | | | **29** | | | **29** | **100.0%** | **5.41 [-48.40, 59.22]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **2.3.2 Lansoprazole group** | | | | | | | | |
| dos Santos 2007 | 323 | 127 | 22 | 269 | 77 | 22 | 35.5% | 54.00 [-8.06, 116.06] |
| Littner 2005 | 381 | 82 | 99 | 381 | 97 | 108 | 64.5% | 0.00 [-24.40, 24.40] |
| **Subtotal (95% CI)** | | | **121** | | | **130** | **100.0%** | **19.15 [-31.48, 69.79]** |

Heterogeneity: Tau² = 879.16; Chi² = 2.52, df = 1 (P = 0.11); I² = 60%
Test for overall effect: Z = 0.74 (P = 0.46)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **2.3.3 Esomeprazole group** | | | | | | | | |
| Kiljander-1 2006 | 342.4 | 127.3 | 111 | 340.3 | 110.3 | 105 | 33.3% | 2.10 [-29.62, 33.82] |
| Kiljander-2 2006 | 335.2 | 123.3 | 173 | 328.7 | 117 | 171 | 52.0% | 6.50 [-18.90, 31.90] |
| Susanto 2008 | 283.7 | 65.9 | 16 | 280.6 | 71.7 | 16 | 14.7% | 3.10 [-44.62, 50.82] |
| **Subtotal (95% CI)** | | | **300** | | | **292** | **100.0%** | **4.53 [-13.77, 22.84]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 2 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.63)

Test for subgroup differences: Chi² = 0.28, df = 2 (P = 0.87), I² = 0%

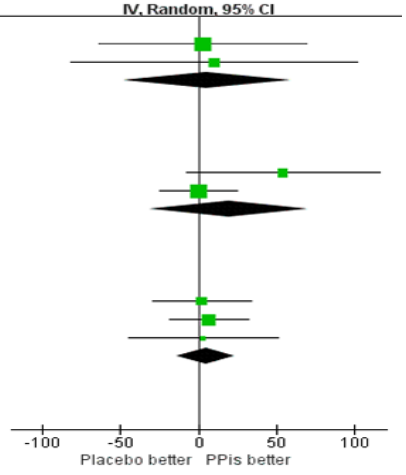


**Figure S3b A,** Trial sequential analysis of evening peak expiratory flow. Heterogeneity adjusted required information size of 1470 subjects calculated in accordance with mean difference of mPEF=20 L/min, "empirical" variance from the meta-analysis of PEF data, α at 0.05, power of 80%, $I^2$ value of 0%. Dashed red cumulative Z curve does not cross solid blue trial sequential monitoring boundaries for benefit or harm, but cross boundaries for futility (blue inner wedge boundaries). Horizontal dotted green lines illustrate traditional level of statistical significance (P=0.05). **B** Forest plot for evening peak expiratory flow in subgroup of the percentage of subjects with symptomatic GERD ≥95%. **C** Forest plot for morning peak expiratory flow in subgroups of treatment duration ≤12 weeks and >12 weeks. **D** Forest plot for evening peak expiratory flow in subgroups of different types of proton pump inhibitors.

**Supplement 4**

No publication reported in $FEV_1$ % predicted (P=0.445). Both sensitivity analysis and egger's test further supported the overall results were stable.

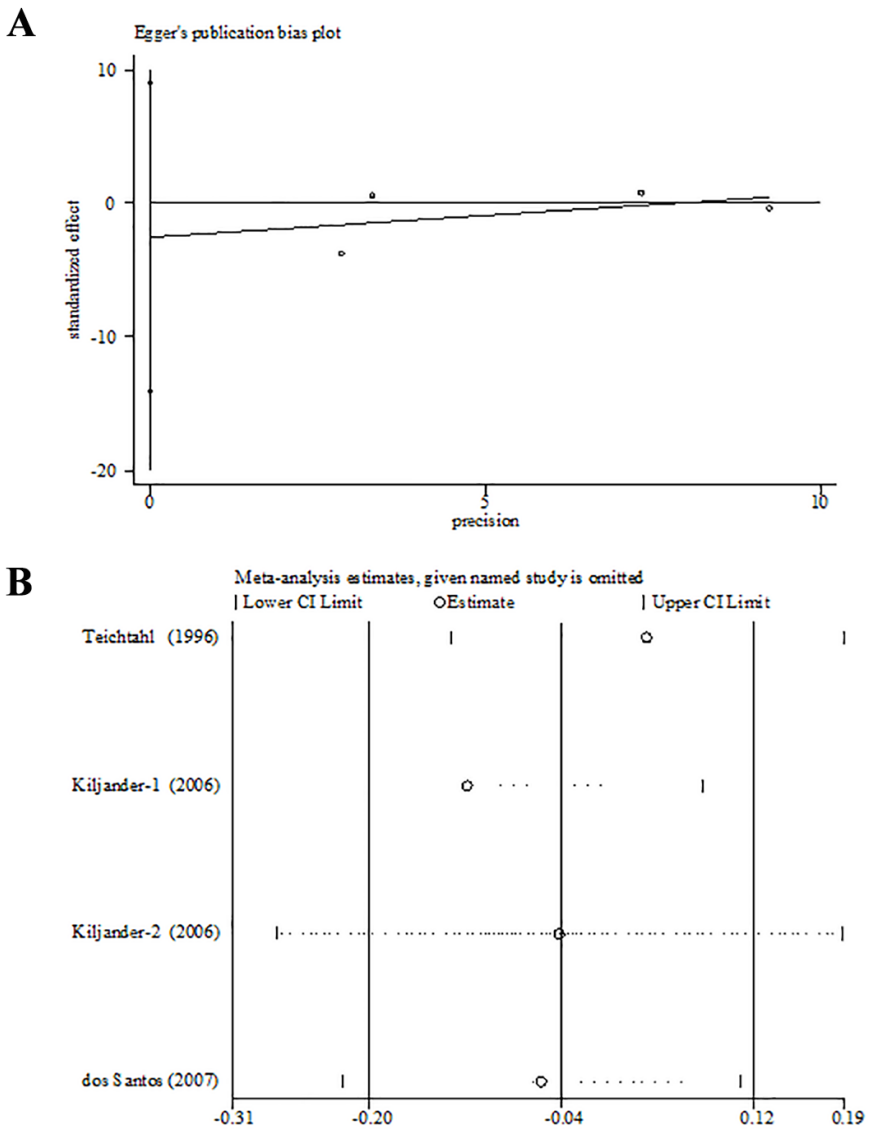



**Figure S4 A,** Egger's publication bias plot for $FEV_1$ % predicted (P=0.445). **B,** Sensitivity analysis for $FEV_1$ % predicted.

**Supplement 5**

No publication reported in asthma symptoms score (P=0.809). Both sensitivity analysis and egger's test further supported the overall results were stable (**supplement 5**).

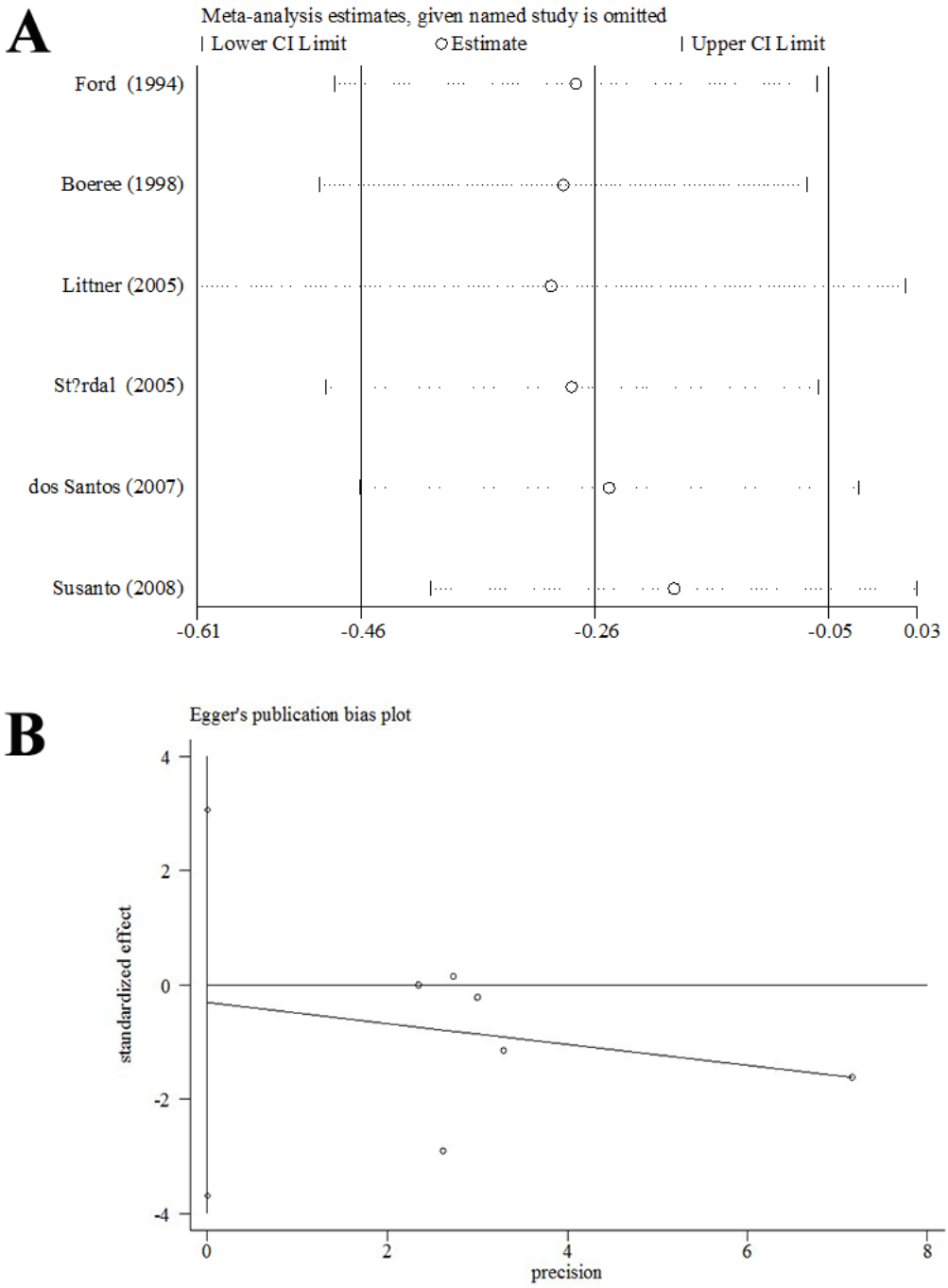



**Figure S5 A,** Egger's publication bias plot for asthma symptoms score (P=0.809). **B,** Sensitivity analysis for asthma symptoms score.

**Supplement 6**

No publication reported in asthma quality of life (P=0.588), but sensitivity analysis showed the results were unstable

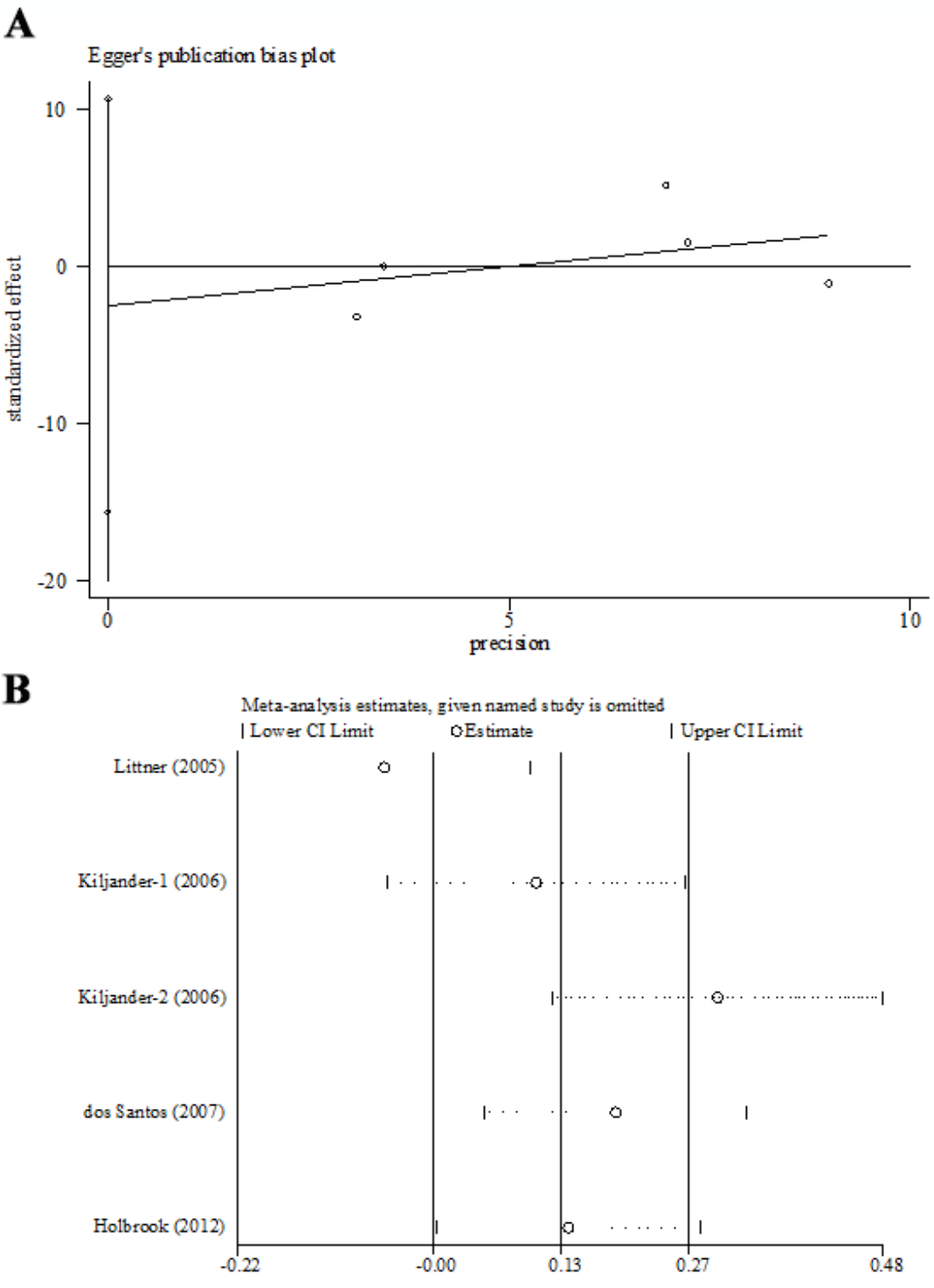



**Figure S6 A,** Egger's publication bias plot for asthma quality of life (P=0.588). **B,** Sensitivity analysis for asthma quality of life.

# PRISMA 2009 Checklist

| 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 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 |
| **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. | 5 |
| 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. | 5-6 |
| 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. | 6, appendix |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 6, appendix |
| 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 |
| 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 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | Appendix |
| 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 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 7 |

# PRISMA 2009 Checklist



| 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). | 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 |
| **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. | 7-8 |
| 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, appendix |
| 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). | 8 |
| 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. | 8-11 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 8-11 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Appendix |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | Appendix |
| **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). | 11-13 |
| 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). | 13 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 13-14 |
| **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. | 14 |

*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(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

# Randomized trials of proton pump inhibitors for gastroesophageal reflux disease in patients with asthma: an updated systematic review and meta-analysis



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|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-043860.R1 |
| Article Type: | Original research |
| Date Submitted by the Author: | 29-May-2021 |
| Complete List of Authors: | Zheng, Zhoude; Peking Union Medical College Hospital, Department of Pulmonary and Critical Care Medicine<br>Luo, Yunyun; Peking Union Medical College Hospital, Department of Endocrinology<br>Li, Jia; Peking Union Medical College Hospital, Department of Pulmonary and Critical Care Medicine<br>Gao, Jinming; Peking Union Medical College Hospital, Department of Pulmonary and Critical Care Medicine |
| Primary Subject Heading: | Respiratory medicine |
| Secondary Subject Heading: | Geriatric medicine, Respiratory medicine |
| Keywords: | Asthma < THORACIC MEDICINE, Oesophageal disease < GASTROENTEROLOGY, THERAPEUTICS |
| | |

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# Randomized trials of proton pump inhibitors for gastroesophageal reflux disease in patients with asthma: an updated systematic review and meta-analysis

Zhoude Zheng[1], Yunyun Luo[2], Jia Li[1], Jinming Gao[1*]

[1]Department of Pulmonary and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China;
[2]Department of Endocrinology, Peking Union Medical College Hospital, Key Laboratory of Endocrinology of National Health Commission, Beijing, China

These authors contributed equally: Zhoude Zheng, Yunyun Luo
*Corresponding author: Jinming Gao, MD, PhD,
Peking Union Medical College Hospital (Dongdan campus), No.1 Shuaifuyuan Wangfujing Dongcheng District, Beijing, China.
E-mail: gjinming@yahoo.com Phone: +86 010 69155049

Key Words: Asthma; gastroesophageal reflux disease; proton pump inhibitors; meta-analysis

Word Count
Abstract: 244 Main Text: 3153

## ABSTRACT

**Objective** Asthma often co-exists with gastroesophageal reflux disease (GERD). The effect of proton pump inhibitors (PPIs) treatment on asthma concomitted with GERD was inconsistent. This study aimed to assess whether PPIs treatment improved morning peak expiratory flow (mPEF) in asthma patients with GERD.

**Data Sources** PubMed, MEDLINE, EMBASE, Web of Science, Cochrane Library and ClinicalTrials.gov; hand searching for reference lists; contacted with authors if necessary.

**Study Selection** All eligible trials were randomized clinical trials comparing PPIs with placebo in asthma patients accompanying with GERD.

**Results** Fourteen randomized clinical trials (2182 participants) were included. Overall, PPIs versus placebo did not affect mPEF in patients with asthma having GERD (weighted mean difference 8.68 L/min, 95% confidence interval [-2.35, 19.37], P=0.11). Trial sequential analysis (TSA) further confirmed this finding (TSA adjusted 95% CI [-1.03, 22.25]). Subgroups analyses based on the percentage of patients with symptomatic GERD ≥95%, treatment duration >12 weeks also found no statistically significant benefit on mPEF. Similarly, analyses of secondary outcomes (evening PEF, forced expiratory volume in 1 second, asthma symptoms score, asthma quality of life score and episodes of asthma exacerbation) did not show significant difference between PPIs and placebo.

**Conclusion** In this meta-analysis, PPIs therapy did not show a statistically significant improvement on mPEF in asthma patients having GERD, neither in subgroup with symptomatic GERD nor in subgroup with treatment duration >12 weeks. This analysis does not support a recommendation for PPIs therapy as empirical treatment in asthma patients with GERD.

**Trial Registration:** PROSPERO CRD42020177330

## Strengths and limitations of this study

- This systematic review strictly followed the methodology recommendations of the Cochrane Handbook, together with a comprehensive literature search.
- This study was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and its study protocol was registered on PROSPERO (CRD42020177330).
- We conducted Trial sequential analysis in our outcomes as well as their subgroups analysis.
- The current study performed a cumulative meta-analysis in all the data.
- Some of the unreported raw data were still unavailable after making extensive efforts to obtain.

## INTRODUCTION

Asthma is a common chronic respiratory disease affecting approximately 300 million people worldwide.[1 2] Gastroesophageal reflux disease (GERD) develops when the reflux of gastric contents causes irritating symptoms or complications, or both.[3] GERD was considered as a trigger factor for asthma. Symptoms and/or diagnosis of GERD presented in 30% to 90% of patients with asthma.[4-6] Association between asthma and GERD has been extensively described elsewhere.[7 8] However, evidence of the causal link between asthma and GERD remains controversial. Some studies have shown that asthma may facilitate the development of GERD by the various mechanisms.[7 8]

PPIs were regarded as the cornerstone of antacid therapy and have been proved effective in empiric treatment of GERD.[9] Given that GERD may be a risk factor for asthma, many randomized controlled trials (RCTs) were performed to identify the efficacy of different types of PPIs in the asthma patients with GERD.[10-23] However, the efficacy of PPIs for the patients with asthma accompanying with GERD has been inconsistent. Previous meta-analyses have pooled the results of PPIs on asthma outcomes in children and adults, but all of them included a small sample size.[24-26] The most recent systematic review examined the efficacy of PPIs treatment for the adults with asthma. However, the review only involved mPEF in subgroup of asthmatic patients diagnosed with GERD, and failed to identify the clinical characteristics of this subgroup population.[27]

Thus, we did a systematic review and meta-analyses to compare the effects PPIs versus placebo on asthma outcomes in the patients with GERD. TSA was performed to quantify the meta-analysis monitoring boundaries and required information size (RIS) for primary outcome. Asthma outcomes included mPEF (primary outcome), evening peak expiratory flow (ePEF), forced expiratory volume in 1 second ($FEV_1$), asthma symptoms score, asthma quality of life, episodes of asthma exacerbation.

## METHOD AND ANALYSIS

The systematic review and meta-analyses were carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The protocol has been registered (CRD42020177330) with International Prospective Register of Systematic Reviews (PROSPERO).

### Eligibility criteria

Types of study

All randomized clinical trials of PPIs in the patients with asthma and GERD were included. The eligible randomized trials were required to report at least one clinical asthma outcome of interest.

Types of participants

Participants with asthma and GERD were eligible for inclusion. There were no restrictions regarding age, gender, and ethnicity. Asthma was diagnosed according to doctor's diagnosis, reported ongoing asthma-related symptoms, evidence of objective measures of lung function. GERD diagnosis based on doctors' diagnosis, reported clinical symptoms of GERD, and objective documentation.

Types of intervention and control

Trials comparing beneficial and harmful effects of PPIs with those of placebo were eligible. This review was restricted to studies with treatment duration of at least 4 weeks.[27] No restrictions were imposed on drug dosage and types of PPIs which contained omeprazole, lansoprazole, pantoprazole, esomeprazole, and rabeprazole. We excluded the trials that focused on the intervention with combination of PPIs and other antacids or gastrointestinal motility regulators.

Outcome measures

This review evaluated the following outcomes: mPEF, ePEF and $FEV_1$, which were commonly used as evidence of variable expiratory airflow obstruction.

Other outcomes included asthma symptoms score (validated questionnaires of all types), asthma quality of life (validated instruments of all types), episodes of asthma exacerbation and adverse events.

**Information sources and search**

A systematic search for evidence on the efficacy of PPIs on patients with asthma was performed through electronic databases, citation search based on reference lists and hand searching of main relevant journals. We did a search in PubMed, EMBASE, Web of Science, Cochrane Library and ClinicalTrials.gov dating from inception to 18th March, 2020. No restrictions were imposed on language, publication date, publication type, or publication status. The search terms and search strategies for all databases were described in the **supplement 1**.

**Study selection**

Two reviewers (ZZ and YL) independently screened titles and abstracts according to the eligibility criteria in an unblinded, standardized manner. Reviews, letters, editorials, case studies, non-human studies, study protocols, non-English-language abstract were excluded during this process. The assessments of eligible full-text articles were carried out independently by two reviewers (ZZ and YL). Disagreements between reviewers were resolved by consensus or referred to a third reviewer (JG) for resolution.

**Data extraction**

Two independent reviewers (ZZ and YL) extracted data from each eligible study by using a pre-designed extraction form. Discrepancies were resolved by consensus or by involvement of a third author (JG). Items of characteristics of included studies were described in **supplement 1**. We contacted the corresponding authors for outcomes data if required.

**Risk of bias in individual studies**

Two independent reviewers (ZZ and YL) evaluated risk of bias according to version 5.1.0 of Cochrane Handbook for Systematic Review of Interventions. An agreement was reached by discussion or by consultation with a third

review author (JG). The domains of evaluation for all the outcomes were selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Each potential source of bias was considered as either “high risk”, “low risk”, or “unclear risk”.

**Statistical analysis**

The weighted mean difference (WMD)/standardized mean difference (SMD) and 95% confidence intervals were calculated for continuous outcomes. The relative risk with 95% confidence intervals was calculated for dichotomous outcomes. Predefined subgroup analysis was undertaken in accordance with patients aged 18 years and older or patients younger than 18 years, the percentage of subjects with symptomatic GERD ≥95%, treatment duration (≤12 weeks VS >12 weeks) and types of PPIs (omeprazole, pantoprazole, lansoprazole, esomeprazole). Given the anticipated variability among patient characteristic and study design, a random effects model with 95% confidence intervals was used in the forest plots (RevMan version 5.3). Statistical heterogeneity was quantified using $I^2$ statistic, with $I^2$ cut-off value of 25%, 50%, and 75% to quantify low, moderate, and high thresholds, respectively. We adopted cumulative meta-analysis in all the data and conducted sensitivity analysis and Egger’s test to identify data stability and publication bias, respectively (StataSE 12.0). TSA (version of 0.9.5.10 Beta) was performed in mPEF and ePEF to quantify meta-analysis monitoring boundaries and RIS using parameters of mean difference of mPEF=20 L/min, estimate variance from the meta-analysis of PEF data, α at 0.05, power of 80%, and $I^2$ value of 0%.

**Patient and Public Involvement**

There was no patient or public involvement in this study.

**RESULTS**

**Study selection and characteristics**

The search strategy yielded 2005 abstracts, of which 49 abstracts were retrieved and under full-articles assessment for eligible articles. All studies conducted lasted for more than 4 weeks. Of these trials, fourteen randomized controlled trials were included, six of which were cross-over studies,[10-12 14 15 20] and eight were of a parallel design.[13 16-19 21-23] The flow diagram for study inclusion is described in **Figure 1**. **Table 1** and **Supplement Table 1** summarizes the characteristics of the included studies (2182 participants) and the characteristics of the subjects, respectively. Of the 14 eligible trials, twelve included subjects aged ≥18 years, while only two aimed at patients aged <18 years (ranged from 6 to 17 years old).[17 23] Mild to severe asthmatics were included. The severity of GERD was reported inconsistently among the trials. Symptoms of heartburn, regurgitation and dysphagia were the common presentations of GERD reported in most studies. The percentage of the subjects with symptomatic GERD was greater than 95% in 8 studies, of which 6 studies reported 100%.[10 11 14 17 20 22]

**Risk of bias within studies**

Each study was assessed in accordance with the Cochrane risk of bias tool (**Figure 2**).[28] Double-blinding method was adopted in all studies except one trial which used a single-blinding fashion.[20] Three trials were supported by pharmaceutical companies.[16 18 22]

**Outcomes**

Fourteen included studies investigated PPIs therapy on patients with asthma and GERD (2182 patients). Asthma outcomes were reported inconsistently among studies, leading to limitation of meta-analysis (**Table 2**). All studies reported one or more outcomes of lung function.

**Primary outcome**

Morning PEF

Only one of the studies with data available found a significant improvement on mPEF.[19] Eight studies containing nine groups were included in meta-analysis (1886 subjects). Among the nine groups, eight showed improvement

in asthma symptoms,[10 12 13 16 18-20 22] but only one group did not cross the neutral (zero) line.[19] The overall analysis found no statistically significant benefit on mPEF with PPIs treatment (8.68 L/min, 95% CI [-2.35, 19.37], P=0.11). Heterogeneity was absent ($I^2$=0%; P=0.73) (**Figure 3 A**). TSA showed a heterogeneity adjusted RIS of 1240 patients without the cumulative Z curve crossing boundaries for benefit or harm (TSA adjusted 95% CI [-1.03, 22.25]), suggesting that PPIs may not show benefit on mPEF of the patients with asthma and GERD (**Figure 4 A**). No publication bias reported in mPEF, and the sensitivity analysis confirmed the robustness of these findings (**Figure S1**).

A subgroup was performed according to the percentage of subjects with symptomatic GERD ≥95% (1253 participants). Of eight eligible studies, five reported available data for meta-analysis.[10 12 16 20 22] No statistically significant effect was found for mPEF in this subgroup (7.07 L/min, 95% CI [-6.56, 20.69], P=0.31) (**Figure 3 B**). TSA showed that only 1158 (79%) of the heterogeneity adjusted RIS of 1470 patients were calculated. However, the cumulative Z curve crossed the boundaries for futility (TSA adjusted 95% CI [-5.94, 25.58]) (**Figure 4 B**).

Next, we conducted subgroups analysis based on duration of PPIs treatment (duration ≤12 weeks with a population of 164 VS >12 weeks with 1722 participants). No statistically significant benefit was demonstrated in both subgroups (duration ≤12 weeks: 23.06 L/min, 95% CI [-3.40, 49.51], P=0.09, P=0.43; duration >12 weeks: 5.87 L/min, 95% CI [-5.83, 17.56], P=0.33) (**Figure 3 C**). Then we conducted TSA in the subgroup with duration >12 weeks. TSA did not alter the efficacy on mPEF with a PPIs treatment duration >12 weeks (TSA adjusted 95% CI [-4.99, 20.50]) (**Figure 4 C**).

Also, three subgroups meta-analyses based on types of PPIs did not showed statistically significant treatment benefit (omeprazole: 88 subjects, 4.65 L/min, 95% CI [-35.43, 44.72], P=0.27; lansoprazole: 251 subjects, 29.18

L/min, 95% CI [-23.21, 81.56], P=0.31; esomeprazole: 1547 subjects, 5.91 L/min, 95% CI [-7.02, 18.84], P=0.37) on mPEF (**Figure 3 D**).

We carried out a cumulative meta-analysis of the effect of PPIs on the mPEF and its subgroups analysis based on the data of publication. However, the effect of PPIs remained unchanged (**Figure S2**).

**Secondary outcomes**

Evening PEF

Ten trials reported ePEF of the subjects with asthma and GERD, of which two trials demonstrated statistically significant improvement on ePEF.[12 18] Of these 10 trials, 6 studies provided information and were included in the meta-analyses (901 participants).[10 12 16 18-20] Meta-analysis did not show statistically significant effect on ePEF (5.58 L/min; 95% CI [-8.19, 19.36]; P=0.43) (**Figure 5 A**). TSA showed that the cumulative Z curve crossed boundaries for futility, suggesting no statistically significant improvement on ePEF with PPIs therapy (TSA adjusted 95% CI [- 6.87, 25.35]). No publication bias reported in ePEF, and the sensitivity analysis showed solid results (**Figure S3a**).

No statistically significant benefit was showed on ePEF by subgroups analyses of the studies in accordance with the percentage of subjects with symptomatic GERD ≥95%, length of PPIs treatment and types of PPIs (**Figure S3b**).

Forced expiratory volume in 1 second

Three studies with a population of 640 provided information of $FEV_1$ % predicted,[12 18 19] and only two with 237 participants provided available data of $FEV_1$ (L),[13 16] which were included in analyses, respectively. At the analysis of $FEV_1$ % predicted, no therapy effect was found on the patients with PPIs use (-1.25%, 95% CI [-4.9, 3.00], P=0.56) (**Figure 5 B1)**. Heterogeneity was substantial ($I^2$=61%; P=0.05). The analysis of the two studies may not demonstrated a benefit on the $FEV_1$ (L) in the patients with PPIs therapy (-0.09 L, 95% CI [-0.28, 0.10], P=0.36) (**Figure 5 B2**). No

publication reported in FEV1 % predicted, the sensitivity analysis showed robust results (**Figure S4**).

Asthma symptoms score

Six studies reported information of asthma symptoms score and were included in meta-analysis (371 participants).[10 13 16 17 19 20] Five of six trials included the patients aged older than 18 years (335 participants). The subgroup of adults showed no statistically significant effect on asthma symptoms score with PPIs treatment (SMD -0.30, 95% CI [-0.61, 0.01], P=0.06, heterogeneity $I^2$=32%, P=0.21). However, the analysis found a small statistically significant improvement on asthma symptoms score (SMD -0.26, 95% CI [-0.52, -0.01], P=0.04), when we pooled the studies in adults and those in children. Heterogeneity was low ($I^2$=19%, P=0.29) (**Figure 5 C**). No publication reported in asthma symptoms score, and the sensitivity analysis showed that the results were robust (**Figure S5**).

Asthma quality of life

Four eligible studies were included for meta-analysis (853 subjects).[16 18 19 23] The result showed no overall effect on the asthma quality of life (SMD 0.01, 95% CI [-0.44, 0.47], P=0.96). Heterogeneity was substantial ($I^2$=89%, P<0.00001) (**Figure 5 D**). No publication bias was reported in this outcome (P=0.588), but sensitivity analysis showed the results were unstable (**Figure S6**). Therefore, the pooled result for asthma quality of life had limited meaning.

Episodes of asthma exacerbation

Only two studies including 1167 patients provided information of episodes of asthma exacerbation and showed an improvement in this variance.[16 22] However, no effect was showed in meta-analysis (relative risk 0.55, 95% CI [0.21, 1.43], P=0.22). Heterogeneity was substantial ($I^2$=81%, P<0.02) (**Figure 5 E**).

Cumulative meta-analysis was performed in all the data of secondary outcomes. Similarly, except a minor improvement on asthma symptoms

score, it was likely that no significant effect was found on ePEF, $FEV_1$ % predicted, asthma quality of life and episodes of asthma exacerbation with the application of PPIs (**Figure S7**).

## DISCUSSION

For primary outcome mPEF, we assessed 8 studies including 9 independent comparisons (1886 participants) and found no statistically significant improvement with PPIs treatment in patients with asthma and GERD compared to placebo. Subgroups analyses according to duration >12 weeks and the percentage of subjects with symptomatic GERD ≥95%, did not demonstrated statistically significant benefit with PPIs therapy. Also, no statistically significant improvement was observed on the secondary outcomes including ePEF, $FEV_1$, asthma symptoms, quality of life and asthma exacerbation. These results were further confirmed by the application of TSA and cumulative meta-analysis.

To enlarge sample size, our analysis not only included trials with asthma subjects having GERD diagnosis for entry criterion, but also those reported GERD subjects in subgroups analyses.[18 20] To the best of our knowledge, this analysis included the largest number of participants to date describing the effect of PPIs treatment in patients with asthma accompanying with GERD. The previous meta-analysis aiming to examine the efficacy of PPIs in the adult patients with asthma, reported a subgroup analysis based on GERD diagnosis for entry criterion with 7 trials (1004 patients).[27] In contrast to our study, a small statistically significant improvement was reported for mPEF in this subgroup, therefore, this analysis might overestimate the benefits on mPEF and exaggerate the effect of positive improvement, because of incomplete and inadequate population inclusion. However, in line with our results, this previous review did not show benefit on in patients with asthma with PPIs treatment on ePEF, $FEV_1$, asthma symptoms score and asthma quality of life.

A study reported that the minimal patient perceivable improvement differences for PEF was 18.79 L/min.[29] The minimal difference in PEF ranging from 15 to 20 L/min were summarized in a review.[30] Our analysis found that the pooled mean difference for mPEF and ePEF were 7.30 and 5.58 L/min respectively, which were far smaller than the minimal effective line, probably showing a lack of evidence to believe the efficacy of PPIs. In alignment with our study, previous meta-analysis published by Cochrane Collaboration found no statistically significant improvement on mPEF and ePEF.[25] Also, a recent large three-arms RCT was consistent with our study.[22]

Several trials have reported that PPIs played no role in asthma patients with asymptomatic GERD, whether in children or adults.[21 23] Similarly, in our subgroup meta-analysis, no statistically significant benefit appeared for mPEF in asthma patients with symptomatic GERD. This result was in keeping with a large trial including all asthma participants with symptomatic GERD.[22] Our subgroup analysis for mPEF based on duration >12 weeks was conducted, suggesting that no improvement appeared with PPIs therapy. In agreement with our result, two large trials did not find improvement for mPEF with PPIs treatment for 24 or 26 weeks.[16 22]

Mechanistically, GERD may trigger asthma via directly damage to the respiratory tree leading to bronchoconstriction by micro-aspiration of gastric or duodenal (or both) contents.[31 32] Previous studies have reported that bile acids and pepsin were found graft failure in lung transplant patients, indicating that acid materials may not be the only one of many irritants in the aspirate during gastroesophageal reflux.[33 34]

PPIs treatment significantly improved asthma symptoms and lung function in patients with exercise-triggered asthma, with asthma and nocturnal respiratory symptoms, or taking LABAs.[18 35] It appeared that benefits of PPIs may be restricted to patients with certain types or status of asthma. Further studies are warranted to examine the pathophysiological mechanism

to determine the causality between asthma and GERD. Notably, if the improvement for asthma conditions were delayed or required more time to present, then the overall effect may be underestimated. Thus, further RCTs should be conducted with a treatment period for more than 6 months. Previous RCTs combined omeprazole and domperidone therapy in patients with asthma and GERD, showing that combined therapy improved asthma symptoms and lung function with treatment period of 12 or 16 weeks.[36 37] Therefore, the efficacy of combined therapy should be further explored. Furthermore, we hopefully expect the effect of genotype-tailored PPIs in patients with asthma and co-morbid GERD.[38]

There are several limitations in the present study. Firstly, we could not extract the data from all the 11 eligible trials reporting mPEF, because of the unavailable reported form (mean difference only,[14] medians and quartiles[15]) or unavailable data in subgroup.[21] However, the overall sample size of these 3 trials was small and we do not think these studies would make a significant difference in our meta-analysis. Secondly, we could not perform a subgroup according to the severity of asthma or GERD as expected, because the severity reported inconsistently and we could not sort out the disease status of each trial. Thirdly, only two RCTs in children were eligible in the present study, making it difficult to evaluate the effect for PPIs on all outcomes in children.[17 23] However, both trials reported no improvement for PPIs in all the asthma outcomes, which were in line with the overall effect in adults in our analysis.

**CONCLUSION**

Compared to placebo, PPIs therapy for asthma patients with GERD did not show statistically significant improvement in mPEF. This futility did not alter in asthma patients neither with symptomatic GERD nor with PPIs treatment for more than 12 weeks. This analysis does not support a recommendation for the empirical use of PPIs therapy in asthma patients having GERD.

**Acknowledgements:**

The authors would like to thank Dr. Xiaoling Li for her suggestions on grammar and vocabularies of this manuscript. We would also like to thank Dr. Xiaorui Lyu (Department of Endocrinology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College) for his advice on data analysis data extraction. This work was supported by the National Natural Science Foundation of China (Grant No. 81970025).

**Author contributions**

ZZ led the meta-analysis was involved at every stage, including protocol development, screening, data extraction, quality assessment, data analysis and manuscript drafting. YL was involved in screening, data extraction, quality assessment, interpretation of results and manuscript revisions. JL facilitated manuscript revisions for important intellectual content. JG supervised this review and was involved in protocol preparation, consensus on disagreement in data extraction, quality assessment, data analysis, interpretation of results, manuscript drafting and revisions.

**Conflicts of interests**

None declared.

**Funding**

This work was supported by the National Natural Science Foundation of China (81970025).

**Patient consent for publication**

Not required.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Data sharing statement**

No additional data are available.

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## List of Figures

**Table 1** Summary of participants characteristics of included studies

| Trials | Mean (SD or range) Age (Years) | Male, n (%) | Severity of asthma | Severity of GERD | Complications of GERD | Symptomatic GERD (%) | Association between asthma and GERD reported |
|---|---|---|---|---|---|---|---|
| Ford 1994 | 63 (50-80) | 5 (50%) | Mean PEFR before and after terbutaline use (SD), 1/minute: 253 (83) and 308 (±94) | Number per grade of esophagitis: Grade I (n=1), Grade II (n=2), Grade III(n=4); Barrett's esophagus (n=2 | Heartburn, regurgitation, lack of proportion | 100% | No |
| Meier 1994 | 49 (34-63) | 9 (60%) | Not stated; inclusion criteria: reversibility of $FEV_1$ and/ or PEF after bronchodilator use: >15% | Number per grade of esophageal inflammation: Grade I (n=1), Grade II (n= 4), Grade III (n= 8), Grade IV (n= 2); hiatal hernia n=10; Barrett's esophagus and peptic stricture n=10 | Not specified | 100% | Yes |
| Teichtahl 1996 | 46 (12) | 12 960% ) | Not stated, inclusion criteria: reversibility of $FEV_1$ >15%; diurnal variation of PEF: >20% | GERD symptoms in all | Not specified | 95% | No |
| Boeree 1998 | 51 (10) | 17 (47.2%) | Mean $FEV_1$ %, pred (SD): Int 66(20); cont 75(23); mPEF mean (SD): Omeprazole group 329 (91); placebo group 321 (109) | Increased gastroesophageal reflux reported in all | Dysphagia Int n=2/1/0, Cont n=3/0/0; heartburn Int n=9/0/0, Cont n=9/3/0; regurgitation Int n=3/0/0, Cont n=4/3/0 | 50% | No |
| Levin 1998 | 57 (35–72) | 6 (67%) | Mean $FEV_1$ (range): 1.9 (1.0–2.9); mean PEFR (range), L/min: mPEF 376 (283–488), ePEF 381 (286–468). | 24-h pH monitoring, mean % time with pH < 4 (range): total: 24.4 (4.7–64.0), supine: 17.6 (0–39.8), upright: 23.8 (5.6–74.4) | Not specified | 100% | No |
| Kiljander 1999 | 49 (21–75) | 18(35%) | Mean PEF (range) L/min, 455 (250 to 700); $FEV_1$% of predicted (range), 81 (31 to 114) | Median % time pH < 4 (75–25% quartiles) : total 9.0 (14.7–5.0), upright 10.1 (15.1–6.9), supine: 4.0 (15.7–0.8) | Not specified | 65% | No |
| Littner 2005 | 47 (12) | 66 (31.9%) | Moderate-to-severe persistent asthma | Mean severity score (SD): Overall reflux symptoms: Int 1.66 (0.69), Cont 1.70 (0.65) ¶ | Patients with symptoms (%): heartburn Int 97%, Cont 95%; regurgitation Int 80%, Cont 80%; dysphagia: Int 32%, Cont 47% | Int 96.1±8.0%, Cont 97.3±5.2% | No |
| Størdal 2005 | 10.2 (9.2), 11.3 (11.0) | 29 (76.3%) | GINA classification of asthma severity (step 1/2/3/4): Int 4/8/7/0, Cont 3/6/10/0. | Reflux index, mean (%, SD): Int 8.8 (4.0), Cont 9.7 (5.1); reflux index≥ 10% (n): Int n=5, Cont n=6 | Not specified | 100% | No |
| Kiljander 2006 — GERD+/NOC+ (Kiljander-1) | 46.3 | 80 (36.5%) | $FEV_1$, % pred: Int 67.3%, Cont 66.2%; Morning PEF, % pred: Int 73.0%, Cont 73.0% | Abnormal 24-h esophageal pH in all | Mean number heartburn symptoms/day: (nighttime) Int 0.42, Cont 0.44; (daytime) Int 0.68, Cont 0.71 | Not stated | Yes |
| Kiljander 2006 — GERD+/NOC- (Kiljander-2) | 44.3 | 94 (26.9%) | $FEV_1$, % pred: Int 65.5%, Cont 67.4%; mPEF, % pred: Int 68.7%, Cont 69.2%. | Abnormal 24-h esophageal pH in all | Mean number heartburn symptoms/day: (nighttime) Int 0.46, Cont 0.47; (daytime) Int 0.68, Cont 0.62 | | |
| dos Santos 2007 | Int 40 (12), Cont 45 (12) | 9 (22.0%) | Mean $FEV_1$% predicted (SD): Int 61.6 (19), Cont 60.4 (19); mean diurnal PEF (SD): Int 317 (13), Cont 264 (86) | Mean GERD symptoms score (SD): Int 12.9 (9), Cont 11.4 (7) | Not specified | 80% | No |
| Susanto 2008 | Int 42.69 (11.11), Cont 37.88 (11.01) | 9 (28.1%) | Moderate persistent asthma; mean $FEV_1$% prediction (SD): Int 72.9 (6.7), Cont 71.2 (7.7); mean PEFR, L/min (SD): Int 258.8 (33.2), Cont 269.5 (76.4) | One or more typical GERD symptoms in all. patients with histopathological esophagitis (%): 87.5% | Heartburn: Int 68%. Cont 87%; atypical chest pain: Int 81.3%, Cont 75%, regurgitation: Int 100%, Cont 100%, dysphagia: Int 12.5%, Cont 25%, water brash: Int 37.5%, Cont 37.5% | 100% | No |
| Mastronarde 2009 | (>18) | Not stated | Persistent and poorly controlled asthma | PH monitoring positive in all | Not specified | 0% | No |
| Kiljander 2010 | 45 (19-70) | 233 (24.3%) | Moderate-to-severe asthma | Moderate severity | Heartburn, acid regurgitation Dyspepsia | 100% | No |
| Holbrook 2012 | (6-17) | Not stated | Poorly controlled asthma | Abnormal 24-h esophageal pH in all | Not specified | 0% | No |

Abbreviations: $FEV_1$, forced expiratory volume in 1 second; mPEF, morning peak expiratory flow; PEFR peak expiratory flow; pred, predicted; PUD, peptic ulcer disease; GERD, gastroesophageal reflux disease; GINA: Global Initiative for Asthma; Int, intervention; Cont, control; PPI, proton pump inhibitor; NOC, nocturnal respiratory symptoms; SD, standard deviation

¶ An investigator-assessed scale was used, as follows: 0, none; 1, mild; 2, moderate; and 3, severe.

**Table 2** Summary of results of PPIs treatment on asthma outcomes

| Trials | mPEF, L/min | ePEF, L/min | $FEV_1$, L | $FEV_1$%, Pred | Asthma symptom score | AQLQ | Episodes of asthma exacerbation |
|---|---|---|---|---|---|---|---|
| Ford 1994 | - | - | NA | NA | - | NA | NA |
| Meier 1994 | NA | NA | - | NA | - | NA | NA |
| Teichtahl 1996 | - | + | NA | - | NA | NA | NA |
| Boeree 1998 | - | - | - | NA | - | NA | NA |
| Levin 1998 | + | - | - | NA | NA | + | NA |
| Kiljander 1999 | - | - | +* | NA | + | NA | NA |
| Littner 2005 | - | - | - | - | - | + | + |
| Størdal 2005 | NA | NA | - | NA | - | - | NA |
| GERD+/NOC-, Kiljander-1 2006 | - | - | NA | - | - | - | NA |
| GERD+/NOC+, Kiljander-2 2006 | + | + | NA | - | - | - | NA |
| dos Santos 2007 | - | - | NA | - | - | + | NA |
| Susanto 2008 | + | - | NA | NA | + | NA | NA |
| Mastronarde 2009 | - | NA | - | NA | - | - | NA |
| Kiljander 2010 | - | - | + | | - | + | + |
| Holbrook 2012 | NA | NA | - | NA | NA | - | NA |

Abbreviations: $FEV_1$, forced expiratory volume in 1 second; pred, predicted; mPEF, morning peak expiratory flow; AQLQ, Asthma Quality of Life Questionnaire; NA, not available; +, significant therapy effect; -, not significant therapy effect.

*, Decline during omeprazole use.

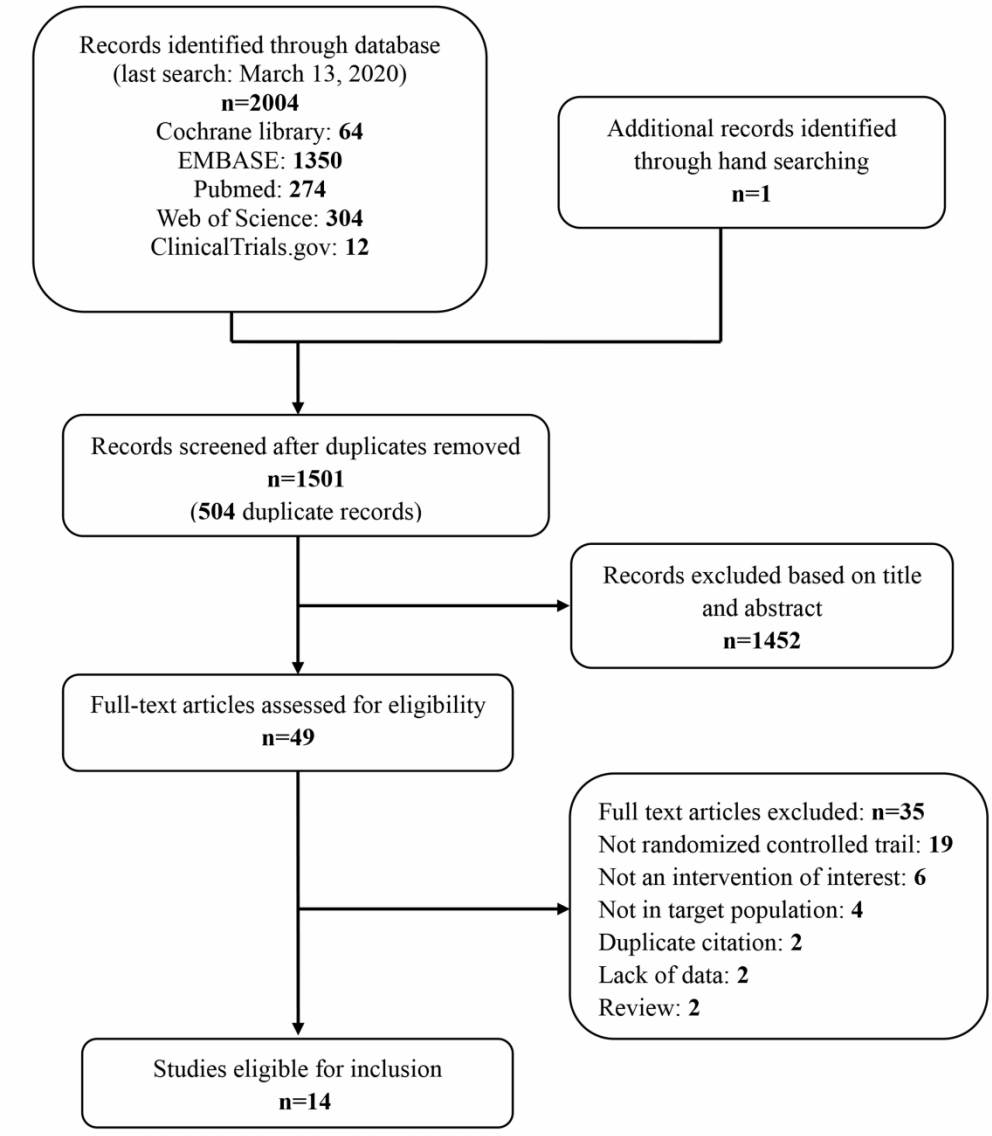


Figure 1 Flow diagram of identification of eligible studies for inclusion.

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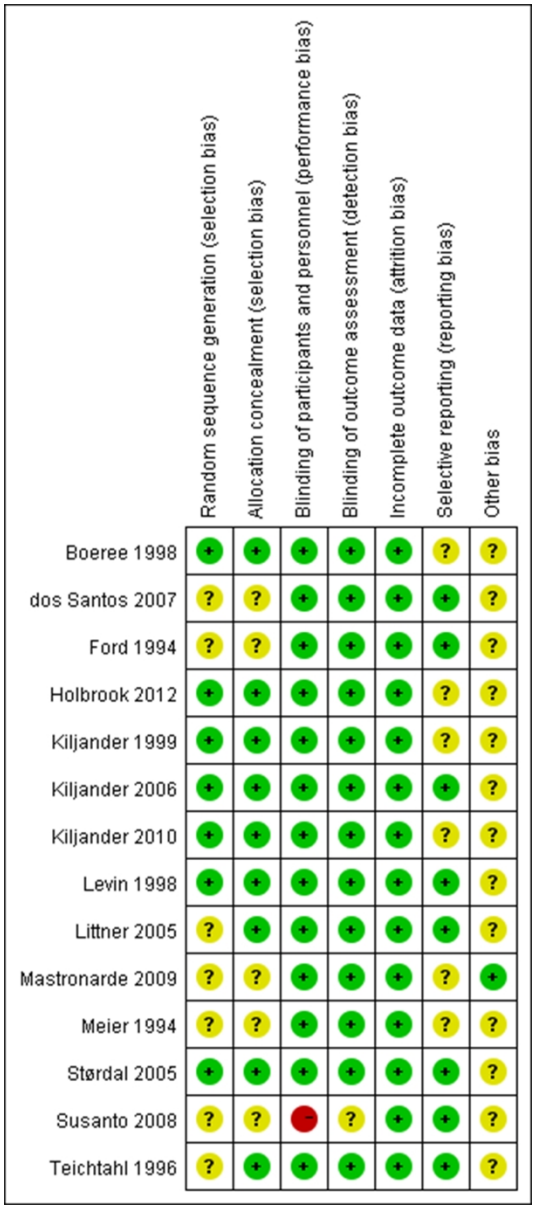


Figure 2 Risk of bias summary displaying review authors' judgements about each risk of bias item for each included study.

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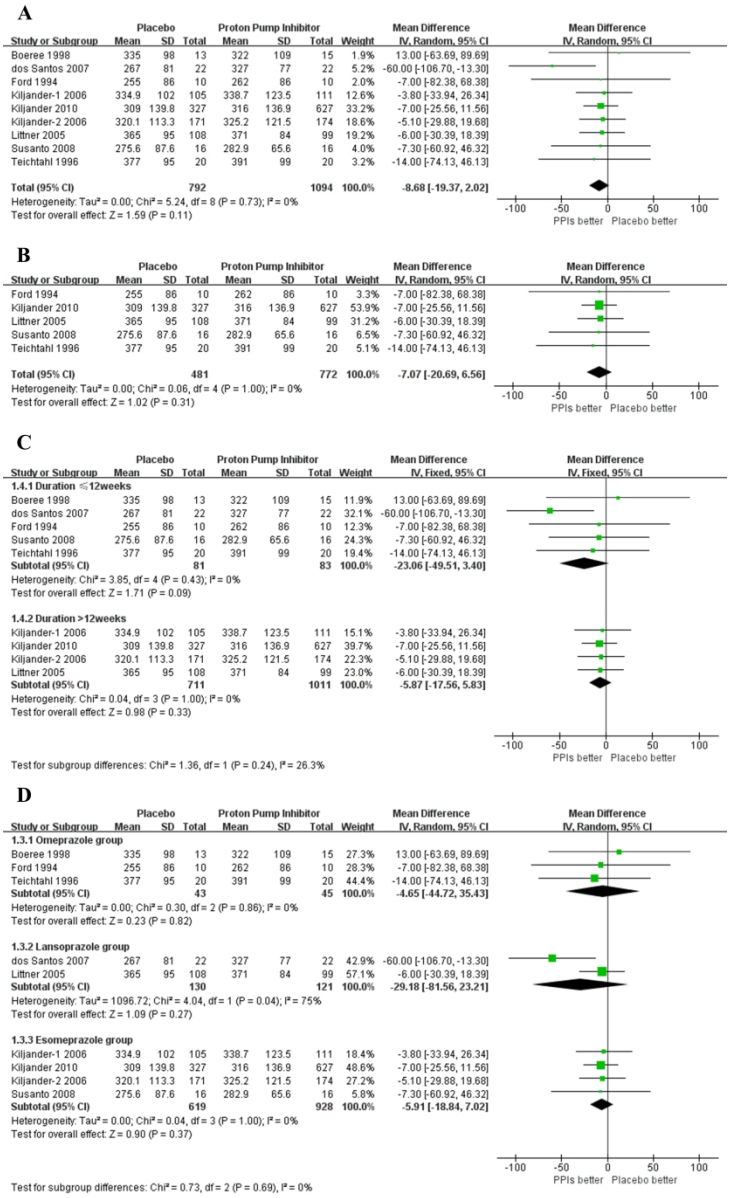


Figure 3 A, Forest plot for morning peak expiratory flow. B, Forest plot for morning peak expiratory flow in subgroup of the percentage of subjects with symptomatic GERD ≥95%. C, Forest plot for morning peak expiratory flow in subgroups of treatment duration ≤12 weeks and >12 weeks. D, Forest plot for morning peak expiratory flow in subgroups of different types of proton pump inhibitors.

1209x1999mm (72 x 72 DPI)

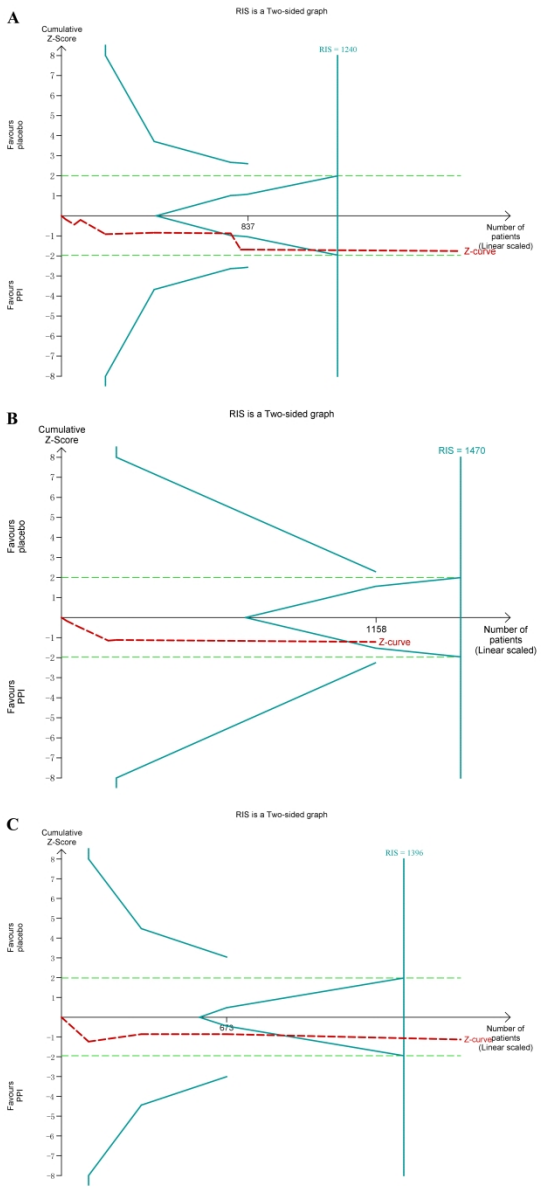


Figure 4 A, Trial sequential analysis of morning peak expiratory flow. B, Trial sequential analysis of morning peak expiratory flow in subgroup of the percentage of subjects with symptomatic GERD ≥95%. C, Trial sequential analysis of morning peak expiratory flow in subgroup of of treatment duration >12 weeks.

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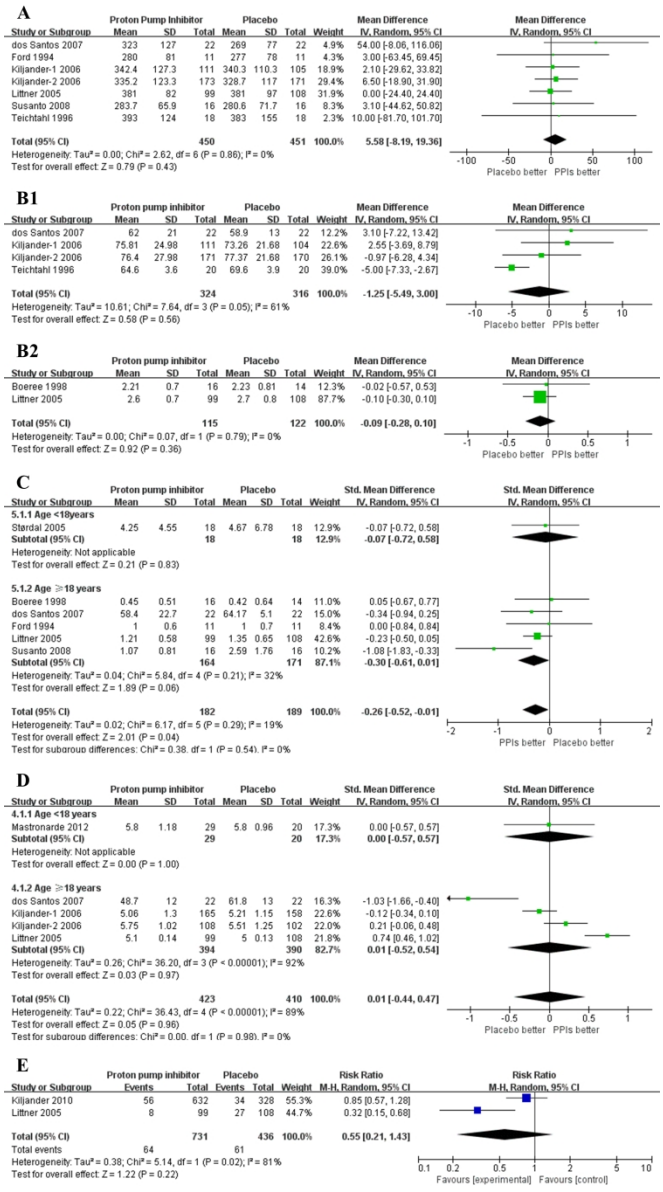



Figure 5 A, Forest plot for evening peak expiratory flow. B1, Forest plot for FEV1 % predicted. B2, Forest plot for FEV1 (L). C, Forest plot for asthma symptoms score. D, Forest plot for asthma quality of life score. E, Forest plot for episodes of asthma exacerbation.

72x133mm (1200 x 1200 DPI)

**Supplement Table 1** Summary of the characteristics of included studies

| Trials | Location | Study design | Medication/dose and usage | Concurrent treatment | Duration (weeks) | Number of Randomized/Completed patients | | Inclusion criteria | | Concurrent disease | Major exclusions |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Intervention group | Control group | Asthma diagnosis | GERD Diagnosis | | |
| Ford 1994 | UK | Crossover | Omeprazole 20 mg, qd | ICS 80%, ipratropium 10% | 4 | Total: 11/10 | | Doctor's diagnosis; reversibility PEFR after bronchodilator use: ≥15%; nocturnal asthma attack | Abnormal pH in 24-h pH monitoring; upper gastrointestinal endoscopy; history of esophagitis | Not stated | Not specified |
| Meier 1994 | America | Crossover | Omeprazole 20 mg, bid | Asthma medications (lack of type), theophylline 11/15 | 6 | Total: 15/15 | | ATS; reversibility of $FEV_1$ and/ or PEF after bronchodilator use: >15% | Abnormal pH in 24-h pH monitoring; manometry; esophagogastroduodenoscopy; acid-perfusion (Bernstein) test | Not stated | ≤18 years old. pregnancy, female unwilling to use birth contraception; unable to give informed consent |
| Teichtahl 1996 | Australia | Crossover | Omeprazole 40 mg, qd | Other asthma medications; Iβ2A | 4 | Total: 25/20 | | Doctor's diagnosis; positive HIT; diurnal variation of PEFR ≥20%; reversibility of $FEV_1$ and/ or PEF after bronchodilator use: >15% | Abnormal pH in 24-h pH monitoring; endoscopy | Not stated | Other significant respiratory disease; respiratory tract infection; significant systemic, esophageal stricture |
| Boeree 1998 | The Netherlands | Parallel | Omeprazole 40 mg, bid | ICS 0.4 mg/day used in all | 12 | 18/16 | 18/14 | Doctor's diagnosis; $FEV_1$ >1.25 L, PC20 <2 mg/mL | Abnormal pH in 24-h pH monitoring, increased GER was defined as >4% of 24 h registration, or >3% during the supine position | COPD | Upper and/or lower respiratory tract infection, other concomitant lung diseases |
| Levin 1998 | America | Crossover | Omeprazole 20 mg, qd | Inhaled β-agonists used in all | 8 | total: 11/9 | | Doctor's diagnosis; ≥15% reversibility in $FEV_1$ after bronchodilator treatment; asthma medication used daily | Symptoms of heartburn or regurgitation at least once weekly without therapy; manometry, ambulatory 24-h esophageal pH monitoring | Not stated | COPD, URTI, prior gastroesophageal surgery, acute PUD, use of omeprazole or URTI within previous 30 days |
| Kiljander 1999 | Finland | Crossover | Omeprazole 40 mg, qd | $Iβ_2A$ 91%; ICS 89% | 8 | total: 57/52 | | Doctor's diagnosis; ATS | 24-h pH monitoring and manometry | Not stated | Not specified |
| Littner 2005 | multi-center, North America | Parallel | Lansoprazole 30 mg, bid | ICS, stable doses of asthma medications for at least 4 wks | 24 | 99/85 | 108/88 | Doctor's diagnosis; $FEV_1$ pred > 50% and < 85%; ≥12% improvement in $FEV_1$ (in liters) after the inhalation of 180 ug of albuterol; five or more nocturnal asthma awakenings and receiving stable doses of asthma medications within previous 4 wks | Investigator judgement based on symptomatic acid reflux and acid-suppressive therapy; 24-h esophageal pH monitoring | Not stated | Smoking; receiving ipratropium bromide, immunotherapy; URTI; uncontrolled medical condition; receiving PPI within 14 days |
| Størdal 2005 | Norway | Parallel | Omeprazole 20 mg, qd | ICS: Int n=17, Cont n=17; long acting bronchodilators: Int 10, Cont 12 | 12 | 19/18 | 19/18 | Doctor's diagnosis; at least two episodes of asthma symptoms requiring medication within previous six months | 24-h pH monitoring; A reflux index ≥5.0 was considered abnormal | Not stated | Previously known or treated GERD |
| Kilja nder 2006 GERD+/ NOC+ (Kiljander-1) | Europe, North America, South America | Parallel | Esomeprazole 40 mg, qd | ICS: 98.6%; LABAs: 49.8% | 16 | 112/105 | 107/105 | $FEV_1$% pred: 50 to 80%, ≥12% (and ≥0.20 L) reversibility; PEF pred <80%; symptom of nighttime awakening with related respiratory symptoms; or PEF | Heartburn ≥2 times/wk; acid regurgitation ≥once /wk within previous 3 month. erosive esophagitis or Barrett's esophagus (without dysplasia) documented in the previous | Not stated | Smoking; esophageal or gastric surgery; glucocorticosteroids <30 days; erosive esophagitis ≤16 wks and PPI use <14 days before enrollment; |
| GERD+/ NOC- | | Parallel | Esomeprazole 40 mg, bid | ICS: 97.7%; LABAs: 34% | 16 | 174/174 | 176/171 | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| (Kiljander-2) | | | | | | | overnight variability ≥15% | 12 months; abnormal 24-h esophageal pH | | recurrent moderate or severe GERD symptoms |
| dos Santos-2007 | Brazil | Parallel | Pantoprazole 40 mg, qd | long-acting β2 -agonists (%): Int 45%, Cont 64%; oral corticoids: Int 9%, Cont 18% | 12 | total: 44 (Int n=22, Cont n=22)/35 | Asthmatic clinical history and symptoms for at least two months; airflow obstruction ($FEV_1$/FVC) < 90% of predicted; the methacholine bronchoprovocation test (+), obstruction reversibility: $FEV_1$ >200 mL and 7% of predicted | 24-h esophageal pH monitoring; manometry | Not stated | Smoking; receiving PPI and H-2 receptor blocker; systemic arterial hypertension |
| Susanto-2008 | Indonesia | Crossover | Esomeprazole 40 mg, qd | inhaled budesonide 400 µg bid, salbutamol 100 mg/puff | 8 | 18/16 | 18/16 | GINA 2002 | Endoscopy and or esophageal histopathologic examination; typical GERD symptoms | Not stated | Not specified |
| Mastronarde-2009 | Multicenter, North America | Parallel | Esomeprazole 40 mg, bid | ICS in all | 24 | 61 /61 | 62 /62 | Doctor's diagnosis; positive methacholine challenge test; 12% increase in $FEV_1$ after bronchodilator treatment | 24-h pH monitoring, mean % time with pH < 4 (range): total >5.8%, upright >8.2%, supine <3.5% | Not stated | Smoking; $FEV_1$% pred <50%; surgery; acid-suppression treatment |
| Kiljander-2010 | Multicenter, Europe, North America, South America | Parallel | Esomeprazole 40 mg, qd/bid | ICS and LABA in all | 26 | 40 mg, qd: 313/273; 40 mg, bid: 320/272 | 328/283 | Doctor's diagnosis; ATS | The validated Reflux Disease Questionnaire, esophageal 24-h pH monitoring | Not stated | Alarm symptoms presented, smoking, esophageal or gastric surgery, Barrett esophagus |
| Holbrook 2012 | America | Parallel | Lansoprazole, children <30 kg: 15 mg/d; children ≥30 kg: 30 mg/d | ICS in all | 24 | 29 /29 | 20 /20 | Doctor's diagnosis; ≥12% in $FEV_1$ after bronchodilator treatment; PC20 ≤16 mg/mL; positive exercise bronchoprovocation test | Ambulatory esophageal pH monitoring: time of pH <4 in 6- to 11-year-old for ≤6%, in 12- to 17-year-old for ≤4% | Not stated | Receiving PPI or other reflux medications; anti-reflux surgery or trachea-esophageal fistula repair; $FEV_1$% pred <60% |

Abbreviations: LABA, long-acting $\beta_2$ -agonists, $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; PC20, provocative concentration of methacholine bromide causing a ≥20% fall in forced expiratory volume in 1 second; I$\beta_2$A, inhaled $\beta_2$ -agonists, ICS, inhaled corticosteroid; mPEF, morning peak expiratory flow; PEFR morning peak expiratory flow; pred, predicted; PUD, peptic ulcer disease; URTI, upper respiratory tract infection; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; GINA: Global Initiative for Asthma; ATS: American Thoracic Society; Int, intervention; Cont, control; wks, weeks; qd, once daily; bid, twice daily; PPI, proton pump inhibitor, NOC, nocturnal respiratory symptoms; SD, standard deviation; HIT histamine bronchoprovocation test; NA, not available

# Appendix

## Supplement 1

## Information sources and search

The search terms of asthma included: “asthma”, “asthma bronchiale”, “asthma pulmonale”, “asthmatic”, “asthmatic subject”, “bronchial asthma”, “bronchus asthma”, “childhood asthma”, “chronic asthma”, “lung allergy” and “asthmatics”.

The search terms of gastroesophageal reflux disease contained: “gastroesophageal reflux”, “gerd”, “gastroesophageal reflux disease”, “gord”, “cardioesophageal reflux”, “esophageal reflux”, “esophageal regurgitation”, “esophagogastric reflux”, “esophagus reflux”, “gastric regurgitation”, “gastro esophageal reflux”, “gastro oesophageal reflux”, “gastroesophageal reflex”, “gastroesophageal regurgitation”, “gastroesophagus reflux”, “gastrooesophageal reflex”, “gastrooesophageal reflux”, “gastrooesophageal reflux disease”, “gastrooesophageal regurgitation”, “oesophageal reflux”, “oesophageal regurgitation”, “oesophagogastric reflux”, and “oesophagus reflux”

The search terms of contained: “proton pump inhibitor”, “proton pump inhibitors”, “PPI” “pantoprazole”, “omeprazole”, “esomeprazole”, “lansoprazole”, and “rabeprazole”.

(search strategies for all databases)

Medline via Ovid, 2020,3,18

| # | Term | Result |
|---|---|---|
| #1 | "randomized controlled trial".pt. | |
| #2 | (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab. | |
| #3 | (retraction of publication or retracted publication).pt. | |
| #4 | or/1-3 | |

| | | |
|---|---|---|
| #5 | (animals not humans).sh. | |
| #6 | ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt. | |
| #7 | (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt. | |
| #8 | 4 not (5 or 6 or 7) | |
| #9 | (asthma$ or bronchial asthma$).ti,ab. | |
| #10 | exp asthma$/ | |
| #11 | exp "gastroesphageal reflux"/ or gastroesophageal reflux.ti,ab,kf. or exp Gastric Acid Reflux/ or exp Gastric Acid Reflux Disease/ or exp gastro-Esophageal Reflux/ or exp Gastro Esophageal Reflux/ or exp Gastroesophageal Reflux Disease/ or exp GERD/ or exp Esophageal Reflux/ or exp Gastro-oesophageal Reflux/ or exp Gastro oesophageal Reflux/ | |
| #12 | (Gastric Acid Reflux or Gastric Acid Reflux Disease or Gastro-Esophageal Refluxor Gastro Esophageal Reflux or Gastroesophageal Reflux Disease or GERD or Esophageal Reflux or Gastro-oesophageal Reflux or Gastro oesophageal Reflux).ti,ab,kf. | |
| #13 | 9 or 10 | |
| #14 | 11 or 12 | |
| #15 | 13 and 14 | |

| | | |
|---|---|---|
| #16 | exp proton pump inhibitor$/ | |
| #17 | exp omeprazole/ or exp lansoprazole/ or exp pantoprazole/ or exp rabeprazole/ or exp esomeprazole/ or exp ilaprazole/ | |
| #18 | (omeprazole or lansoprazole or pantoprazole or rabeprazole or esomeprazole or ilaprazole or proton pump inhibitor$).ti,ab,kf. | |
| #19 | 16 and 17 and 18 | |
| #20 | 8 and 15 and 19 | 12 |

Pubmed 2020,3,18

| # | Term | Result |
|---|---|---|
| #1 | Search "Asthma"[Mesh] | 126238 |
| #2 | Search "asthma*"[Title/Abstract] | 146574 |
| #3 | Search “Bronchial Asthma”[Title/Abstract] | 18297 |
| #4 | Search (((((("asthma bronchiale"[Title/Abstract]) OR "asthma pulmonale"[Title/Abstract]) OR "asthmatic"[Title/Abstract]) OR "asthmatics"[Title/Abstract]) OR "bronchus asthma"[Title/Abstract]) OR "childhood asthma"[Title/Abstract]) OR " chronic asthma"[Title/Abstract]) OR "lung allergy"[Title/Abstract] | 42241 |
| #5 | #1 OR #2 OR #3 OR #4 | 175686 |
| #6 | Search "Gastroesophageal Reflux"[Mesh] | 26315 |
| #7 | Search ((((((((((((((((((("gastroesophageal reflux"[Title/Abstract]) OR "gerd"[Title/Abstract]) OR | 26101 |

| | | |
|---|---|---|
| | "gastroesophageal reflux disease"[Title/Abstract]) OR "gord"[Title/Abstract]) OR "cardioesophageal reflux"[Title/Abstract]) OR "esophageal reflux"[Title/Abstract]) OR "esophageal regurgitation"[Title/Abstract]) OR "esophagogastric reflux"[Title/Abstract]) OR "esophagus reflux"[Title/Abstract]) OR "gastric regurgitation"[Title/Abstract]) OR "gastro esophageal reflux"[Title/Abstract]) OR "gastro oesophageal reflux"[Title/Abstract]) OR "gastroesophageal reflex"[Title/Abstract]) OR "gastroesophageal regurgitation"[Title/Abstract]) OR "gastroesophagus reflux"[Title/Abstract]) OR "gastrooesophageal reflex"[Title/Abstract]) OR "gastrooesophageal reflux"[Title/Abstract]) OR "gastrooesophageal reflux disease"[Title/Abstract]) OR "gastrooesophageal regurgitation"[Title/Abstract]) OR "oesophageal reflux"[Title/Abstract]) OR "oesophageal regurgitation"[Title/Abstract]) OR "oesophagogastric reflux"[Title/Abstract]) OR "oesophagus reflux"[Title/Abstract] | |
| #8 | #6 OR #7 | 35248 |
| #9 | #5 AND #8 | 2083 |
| #10 | Search "Proton Pump Inhibitors"[Mesh] | 10998 |
| #11 | Search "proton pump inhibitors"[Title/Abstract] | 8793 |
| #12 | Search (((((("omeprazole"[Title/Abstract]) OR | 12476 |

| | | |
|---|---|---|
| | "lansoprazole"[Title/Abstract]) OR "pantoprazole"[Title/Abstract]) OR "rabeprazole"[Title/Abstract]) OR "esomeprazole"[Title/Abstract]) OR "ilaprazole"[Title/Abstract] | |
| #13 | #10 OR #11 OR #12 | 23677 |
| #14 | #9 AND #10 | 274 |

Embase 3,18,2020

| # | Term | Result |
|---|---|---|
| #1 | ('asthma'/exp OR 'asthma' OR 'asthma bronchiale' OR 'asthma pulmonale' OR 'asthma, bronchial' OR 'asthmatic' OR 'asthmatic subject' OR 'bronchial asthma' OR 'bronchus asthma' OR 'childhood asthma' OR 'chronic asthma' OR 'lung allergy') AND ('gastroesophageal reflux'/exp OR 'gerd (gastroesophageal reflux disease)' OR 'gerd (gastrooesophageal reflux disease)' OR 'gord (gastrooesophageal reflux disease)' OR 'cardioesophageal reflux' OR 'cardiooesophageal reflux' OR 'esophageal reflux' OR 'esophageal regurgitation' OR 'esophagogastric reflux' OR 'esophagus reflux' OR 'gastric regurgitation' OR 'gastro esophageal reflux' OR 'gastro oesophageal reflux' OR 'gastroesophageal reflex' OR 'gastroesophageal reflux' OR 'gastroesophageal reflux disease' OR 'gastroesophageal regurgitation' OR 'gastroesophagus reflux' OR 'gastrooesophageal reflex' OR 'gastrooesophageal reflux' OR | 858 |

| | | |
|---|---|---|
| | 'gastrooesophageal reflux disease' OR 'gastrooesophageal regurgitation' OR 'oesophageal reflux' OR 'oesophageal regurgitation' OR 'oesophagogastric reflux' OR 'oesophagus reflux' OR 'reflux, gastroesophageal' OR 'reflux, gastrooesophageal' OR 'regurgitation, gastric' OR 'regurgitation, gastroesophageal' OR 'regurgitation, gastrooesophageal') AND ('proton pump inhibitors':ti,ab OR 'lansoprazole'/exp OR '2 [ [[3 methyl 4 (2, 2, 2 trifluoroethoxy) 2 pyridyl] methyl] sulfinyl] 1h benzimidazole' OR 'a 65006' OR 'a65006' OR 'abt 006' OR 'abt006' OR 'ag 1749' OR 'ag1749' OR 'agopton' OR 'bamalite' OR 'banilux' OR 'betalans' OR 'compraz' OR 'dakar (drug)' OR 'daxar' OR 'dostab' OR 'duomate' OR 'ilsatec' OR 'inhipraz' OR 'keval' OR 'lancid' OR 'lancopen' OR 'langaton' OR 'lanpra' OR 'lanpraz' OR 'lanprol' OR 'lanproton' OR 'lansazol' OR 'lansobene' OR 'lansol' OR 'lansone' OR 'lansop' OR 'lansopep' OR 'lansoprazol' OR 'lansoprazole' OR 'lansox' OR 'lansozole' OR 'lanster' OR 'lanston' OR 'lanvell' OR 'lanximed' OR 'lanzo' OR 'lanzol-30' OR 'lanzopral' OR 'lanzoprazole' OR 'lanzor' OR 'lanzul' OR 'lapraz' OR 'laprazol' OR 'laproton' OR 'lasgan' OR 'limpidex' OR 'lopral' OR 'monolitum' OR 'ogast' OR 'ogasto' OR 'ogastoro' OR 'ogastro' OR 'opiren' OR 'pampe' OR 'praton' OR 'prevacid' OR 'prevacid 24 hr' OR 'prevacid fastab' OR 'prevacid iv' OR 'prevacid solutab' OR 'prezal' OR 'prolanz' OR 'prosogan' OR 'pysolan' OR 'sopralan-30' OR 'suprecid' OR 'takepron' OR | |

| | | |
|---|---|---|
| | 'takepron od' OR 'tanzolan' OR 'ulpax' OR 'zoton' OR 'zoton fastab' OR 'omeprazole'/exp OR '5 methoxy 2 [ [(4 methoxy 3, 5 dimethyl 2 pyridyl) methyl] sulfinyl] benzimidazole' OR 'aleprozil' OR 'antra' OR 'antra mups' OR 'arapride' OR 'audazol' OR 'baromezole' OR 'desec' OR 'dolintol' OR 'domer' OR 'dudencer' OR 'duogas' OR 'emeproton' OR 'epirazole' OR 'ezipol' OR 'gasec' OR 'gasec gastrocaps' OR 'gastec' OR 'gastop' OR 'gastrimut' OR 'gastrolac' OR 'gastroloc' OR 'glaveral' OR 'h 168 68' OR 'h 168-68' OR 'h-etom' OR 'h168 68' OR 'h168-68' OR 'hovizol' OR 'hyposec' OR 'inhibitron' OR 'inhipump' OR 'logastric' OR 'lomac' OR 'lopraz' OR 'losamel' OR 'losec' OR 'losec mups' OR 'losecosan' OR 'ludea' OR 'madiprazole' OR 'maxor' OR 'medoprazole' OR 'medral' OR 'meiceral' OR 'mepral' OR 'mepzol' OR 'mezzopram' OR 'miol' OR 'miracid' OR 'mopral' OR 'mopralpro' OR 'nocid' OR 'ocid' OR 'ogal' OR 'olexin' OR 'omedar' OR 'omelon' OR 'omep uno' OR 'omepral' OR 'omeprazen' OR 'omeprazol' OR 'omeprazole' OR 'omeprazole magnesium' OR 'omeprazole sodium' OR 'omeprazon' OR 'omepril' OR 'omeraz' OR 'omesec' OR 'omestad' OR 'omezin' OR 'omezol' OR 'omezolan' OR 'omezole' OR 'omezzol' OR 'omisec' OR 'omizac' OR 'omolin' OR 'ompranyt' OR 'omprazole' OR 'onexal' OR 'oprax' OR 'ozoken' OR 'parizac' OR 'penrazole' OR 'pepticum' OR 'peptidin' OR 'peptilcer' OR 'peptizole' OR 'pra-sec' OR 'prazidec' OR 'prazole' | |

| | | |
|---|---|---|
| | OR 'prilosec' OR 'prilosec otc' OR 'prisolec' OR 'probitor' OR 'proceptin' OR 'protoloc' OR 'ramezol' OR 'rapinex' OR 'reglacid' OR 'result (drug)' OR 'risek' OR 'romep' OR 'roweprazol' OR 'secrepina' OR 'severon' OR 'stomacer' OR 'stomec' OR 'stozole' OR 'suifac' OR 'ulceral' OR 'ulcozol' OR 'ulnor' OR 'ulsek' OR 'ulsen' OR 'ulzol' OR 'vulcasid' OR 'wonmp' OR 'xoprin' OR 'zatrol' OR 'zefxon' OR 'zenpro' OR 'zimor' OR 'zoltum' OR 'pantoprazole'/exp OR '5 difluoromethoxy 2 [ (3, 4 dimethoxy 2 pyridyl) methylsulfinyl] 1h benzimidazole' OR 'anagastra' OR 'branzol' OR 'by 1023' OR 'by1023' OR 'controloc' OR 'controloc control' OR 'eupantol' OR 'inipom' OR 'inipomp' OR 'pantecta' OR 'pantecta control' OR 'pantodac' OR 'pantodar' OR 'pantoloc' OR 'pantoloc control' OR 'pantop' OR 'pantoprazole' OR 'pantoprazole sodium' OR 'pantoprazole sodium sesquihydrate' OR 'pantozol' OR 'pantozol control' OR 'pepticus' OR 'protium' OR 'protonix' OR 'protonix iv' OR 'rifun' OR 'rifun 40' OR 'sk and f 96022' OR 'skf 96022' OR 'skf96022' OR 'somac' OR 'somac control' OR 'ulcepraz' OR 'ulcotenal' OR 'ziprol' OR 'zurcal' OR 'zurcale' OR 'zurcazol' OR 'rabeprazole'/exp OR '2 [ [4 (3 methoxypropoxy) 3 methyl 2 pyridyl] methylsulfinyl] benzimidazole' OR 'aciphex' OR 'aciphex sprinkle' OR 'dexrabeprazole' OR 'e 3810 (benzimidazole derivative)' OR 'e3810 (benzimidazole derivative)' OR 'ly 307640' OR 'ly307640' OR 'pariet' OR 'pariprazole' OR 'pariprazole sodium' OR 'rabec' | |

| | | |
|---|---|---|
| | OR 'rabeloc' OR 'rabeprazole' OR 'rabeprazole sodium' OR 'esomeprazole'/exp OR 'esomeprazol' OR 'esomeprazole' OR 'esomeprazole magnesium' OR 'esomeprazole potassium' OR 'esomeprazole sodium' OR 'esoprax' OR 'h 199 18' OR 'h 199-18' OR 'h 19918' OR 'h199 18' OR 'h199-18' OR 'h19918' OR 'inexium' OR 'nexium' OR 'nexium 24hr' OR 'nexium control' OR 'nexium iv' OR 'nexium-mups' OR 'perprazole' OR 'sompraz' OR 'ilaprazole'/exp OR '2 [ (4 methoxy 3 methyl 2 pyridyl) methylsulfinyl] 5 (1 pyrrolyl) 1h benzimidazole' OR 'ilaprazole' OR 'iy 81149' OR 'iy81149') | |
| #2 | 'asthma*':ab,ti OR 'asthma bronchiale':ab,ti OR 'asthma pulmonale':ab,ti OR 'asthmatic':ab,ti OR 'asthmatics':ab,ti OR 'asthmatic subject':ab,ti OR 'bronchial asthma':ab,ti OR 'bronchus asthma':ab,ti OR 'childhood asthma':ab,ti OR 'chronic asthma':ab,ti OR 'lung allergy':ab,ti | 230139 |
| #3 | 'asthma'/exp OR asthma | 321680 |
| #4 | #2 OR #3 | 324305 |
| #5 | 'gastroesophageal reflux'/exp OR 'gastroesophageal reflux' | 66642 |
| #6 | 'gastroesophageal reflux':ab,ti OR 'gerd':ab,ti OR 'gastroesophageal reflux disease':ab,ti OR 'gord':ab,ti OR 'cardioesophageal reflux':ab,ti OR 'esophageal reflux':ab,ti OR 'esophageal regurgitation':ab,ti OR 'esophagogastric reflux':ab,ti OR 'esophagus reflux':ab,ti OR 'gastric regurgitation':ab,ti OR 'gastro esophageal reflux':ab,ti | 41444 |

| | | |
|---|---|---|
| | OR 'gastro oesophageal reflux':ab,ti OR 'gastroesophageal reflex':ab,ti OR 'gastroesophageal regurgitation':ab,ti OR 'gastroesophagus reflux':ab,ti OR 'gastrooesophageal reflex':ab,ti OR 'gastrooesophageal reflux':ab,ti OR 'gastrooesophageal reflux disease':ab,ti OR 'gastrooesophageal regurgitation':ab,ti OR 'oesophageal reflux':ab,ti OR 'oesophageal regurgitation':ab,ti OR 'oesophagogastric reflux':ab,ti OR 'oesophagus reflux':ab,ti | |
| #7 | #5 OR #6 | 70399 |
| #8 | #4 AND #7 | 5602 |
| #9 | 'omeprazole'/exp OR 'proton pump inhibitor'/exp OR 'lansoprazole'/exp OR 'pantoprazole'/exp OR 'rabeprazole'/exp OR 'esomeprazole'/exp OR 'ilaprazole'/exp | 76773 |
| #10 | 'omeprazole':ab,ti OR 'proton pump inhibitor':ab,ti OR 'lansoprazole':ab,ti OR 'pantoprazole':ab,ti OR 'rabeprazole':ab,ti OR 'esomeprazole':ab,ti OR 'ilaprazole':ab,ti | 27726 |
| #11 | #9 OR #10 | 78726 |
| #12 | #8 AND #11 | 1328 |
| #13 | #1 OR #12 | 1350 |

Note: #1 Retrieval strategy was through “PICO” in Embase.

Web of science 18,3,2020

| # | Term | Result |
|---|---|---|
| #1 | TS=(“gastroesophageal reflux”) OR TS=(“gerd ‘:ab,ti OR ‘gastroesophageal reflux disease”) OR TS=(“gord ‘:ab,ti OR ‘cardioesophageal reflux”) OR TS=(“esophageal reflux”) OR TS=(“esophageal regurgitation”) OR TS=(“esophagogastric reflux”) OR TS=(“esophagus reflux”) OR TS=(“gastric regurgitation”) OR TS=(“gastro esophageal reflux”) OR TS=(“gastro oesophageal reflux”) OR TS=(“gastroesophageal reflex”) OR TS=(“gastroesophageal regurgitation”) OR TS=(“gastroesophagus reflux”) OR TS=(“gastrooesophageal reflex”) OR TS=(“gastrooesophageal reflux”) OR TS=(“gastrooesophageal reflux disease”) OR TS=(“gastrooesophageal regurgitation”) OR TS=(“oesophageal reflux”) OR TS=(“oesophageal regurgitation”) OR TS=(“oesophagogastric reflux”) OR TS=(“oesophagus reflux”) | |
| #2 | TS=(“asthma*”) OR TS=(“asthma bronchiale”) OR TS=(“asthma pulmonale”) OR TS=(“asthmatic”) OR TS=(“asthmatics”) OR TS=(“asthmatic subject”) OR TS=(“bronchial asthma”) OR TS=(“bronchus asthma”) OR TS=(“childhood asthma”) OR TS=(“chronic asthma”) OR TS=(“lung allergy”) | |
| #3 | #2 AND #1 | |
| #4 | TS=("omeprazole") OR TS=("proton pump inhibitor*") OR TS=("lansoprazole") OR TS=("pantoprazole") OR | |

| | | |
|---|---|---|
| | TS=("rabeprazole") OR TS=("esomeprazole") OR TS=("ilaprazole") | |
| #5 | #4 AND #3 | 304 |

Cochrane library 18,3,2020

| # | Term | Result |
|---|---|---|
| #1 | MeSH descriptor: [Asthma] explode all trees | |
| #2 | MeSH descriptor: [Gastroesophageal Reflux] explode all trees | |
| #3 | (“asthma” OR “asthma bronchiale” OR “asthma pulmonale” OR “asthmatic” OR “asthmatic subject” OR “bronchial asthma” OR “bronchus asthma” OR “childhood asthma” OR “chronic asthma” OR “lung allergy” OR “asthmatics”):ti,ab,kw | |
| #4 | (“gastroesophageal reflux” OR “gerd “ OR “gastroesophageal reflux disease” OR “gord “ OR “cardioesophageal reflux” OR “esophageal reflux” OR “esophageal regurgitation” OR “esophagogastric reflux” OR “esophagus reflux” OR “gastric regurgitation” OR “gastro esophageal reflux” OR “gastro oesophageal reflux” OR “gastroesophageal reflex” OR “gastroesophageal regurgitation” OR “gastroesophagus reflux” OR “gastrooesophageal reflex” OR “gastrooesophageal reflux” OR “gastrooesophageal reflux disease” OR “gastrooesophageal regurgitation” OR “oesophageal reflux” OR “oesophageal regurgitation” OR “oesophagogastric reflux” OR “oesophagus reflux”):ti,ab,kw | |

| | | |
|---|---|---|
| #5 | #1 OR #3 | |
| #6 | #2 OR #4 | |
| #7 | #5 AND #6 | |
| #8 | MeSH descriptor: [Proton Pump Inhibitors] explode all trees | |
| #9 | ("proton pump inhibitors"):ti,ab,kw | |
| #10 | MeSH descriptor: [Esomeprazole] explode all trees | |
| #11 | ("esomeprazole"):ti,ab,kw | |
| #12 | ("omeprazole" OR "lansoprazole" OR "pantoprazole" OR "rabeprazole" OR "esomeprazole" OR "ilaprazole"):ti,ab,kw | |
| #13 | MeSH descriptor: [Lansoprazole] explode all trees | |
| #14 | MeSH descriptor: [Pantoprazole] explode all trees | |
| #15 | MeSH descriptor: [Rabeprazole] explode all trees | |
| #16 | #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 | |
| #17 | #7 AND #16 | 63 |

Clinical trail (US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov)18,3,2020

Retrieval strategy:

"Proton Pump Inhibitors" OR "omeprazole" OR "lansoprazole" OR "pantoprazole" OR "rabeprazole" OR "esomeprazole" OR "ilaprazole" | Completed Studies | "asthma" and "gastroesophageal reflux"

Applied Filters: Completed

Results: 12

**Data extraction**

Data of the included studies characteristics were collected if available. (a) Items of characteristics of included studies contained study location, study design, medication type/dose/usage, concurrent treatment, treatment duration, randomized and completed sample size, diagnostic inclusion criteria of asthma and GERD, concurrent diseases, major exclusions; (b) items of subject characteristics included age, male proportion, severity of asthma and GERD, complications of GERD, proportion of symptomatic GERD, and whether the association between asthma and GERD were reported; (c) items of effect of each outcome mentioned above included mean, standard deviation (SD), 95% confidence interval, median, interquartile range, and/or range.

If trials reported more than one eligible comparison group (for example, intervention group-1 VS control group-1 and intervention group-2 VS control group-2), these were considered independent studies and these data were extracted respectively if available. Three-arm trials (for example, two intervention groups VS control group) were combined appropriately into one PPI group and one placebo group.

**Supplement 2**

No publication bias reported in mPEF (P=0.342). Both sensitivity analysis and egger's test further supported the overall results were stable.

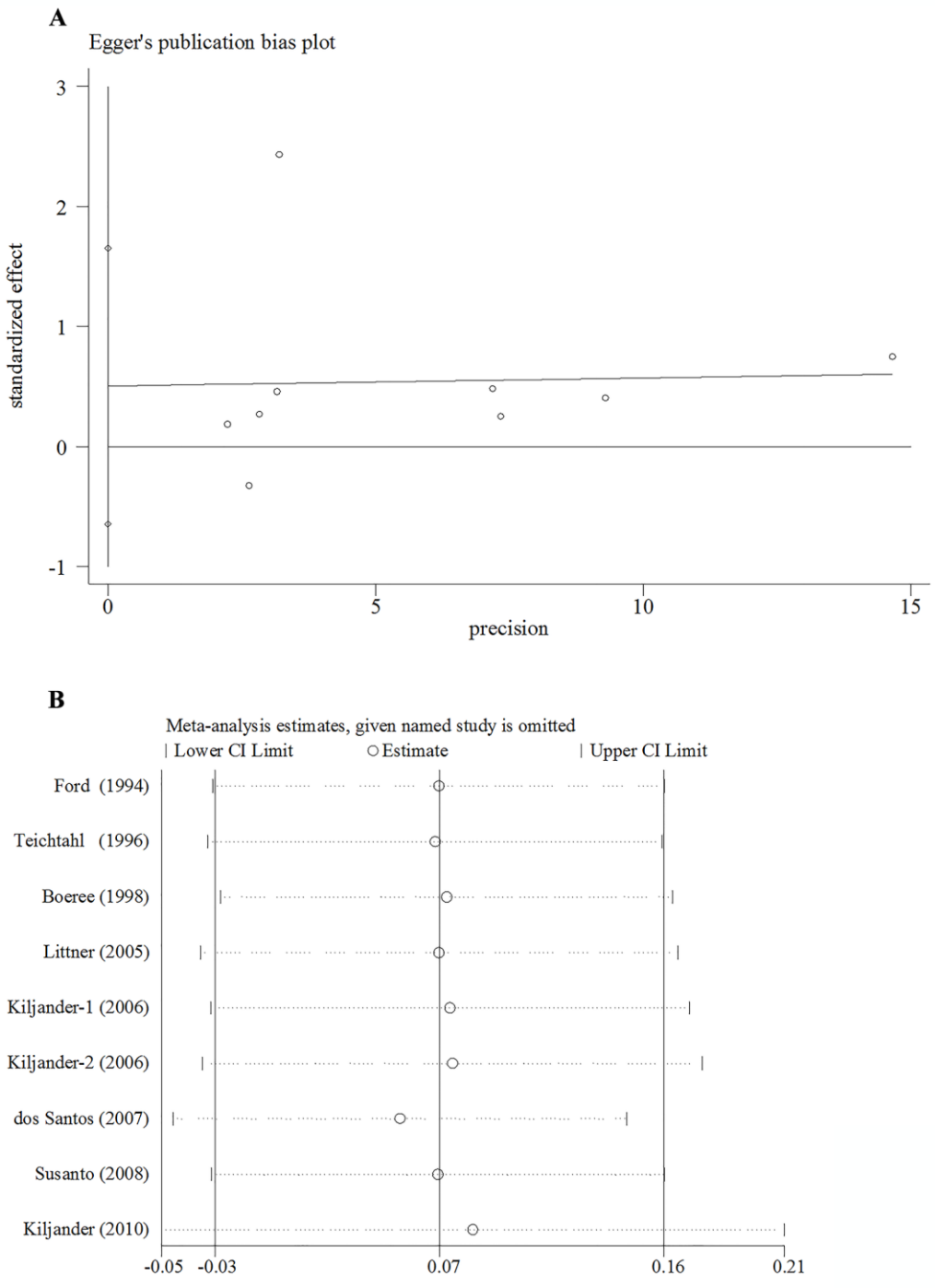



**Figure S1 A,** Egger's publication bias plot for mPEF (P=0.336). **B,** Sensitivity analysis for mPEF.

**Supplement 3**

Results of cumulative meta-analysis of mPEF and its subgroups analysis showed no significant improvement with the application of PPIs.

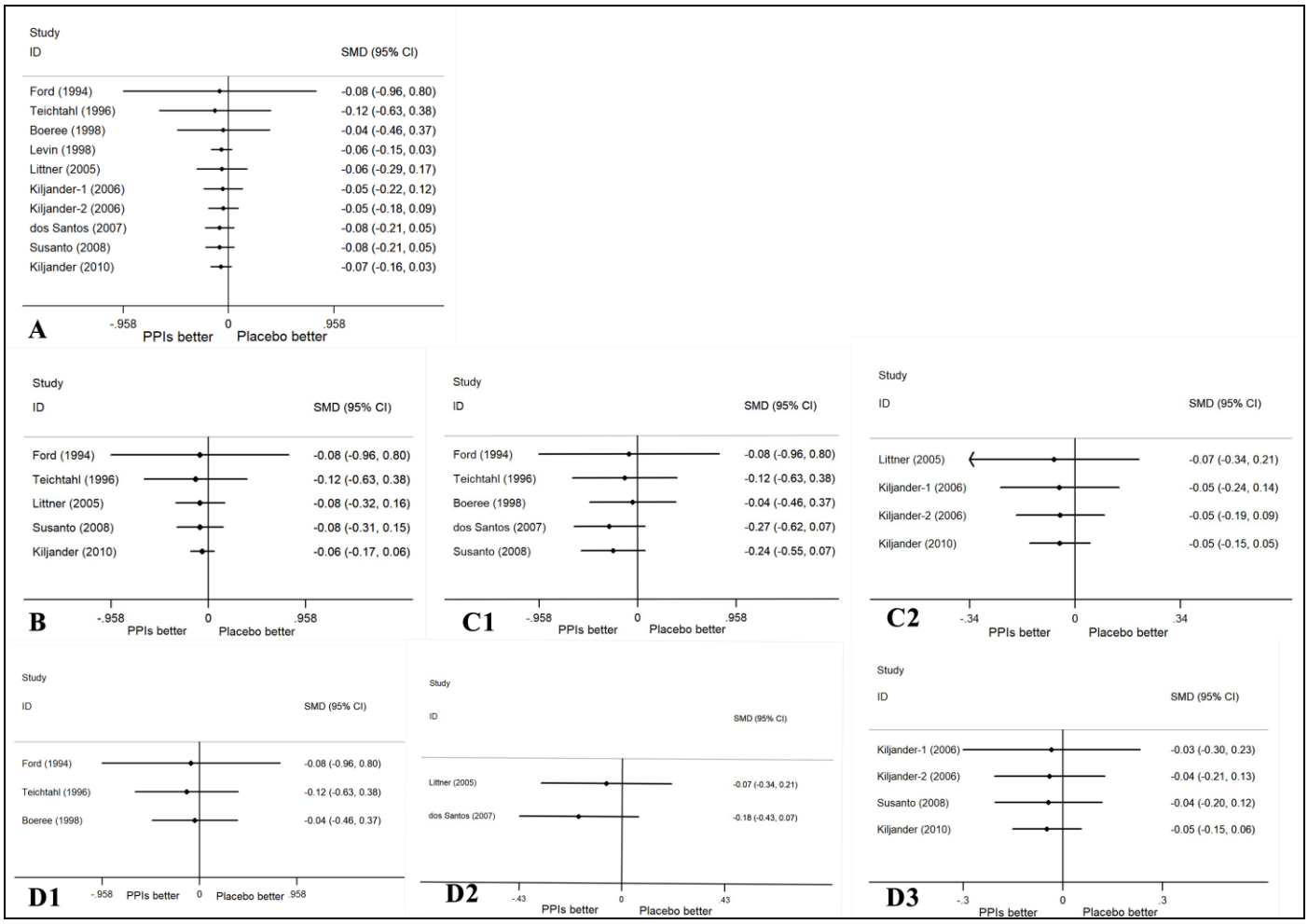



**Figure S2 A,** Cumulative meta-analysis of morning peak expiratory flow. **B,** Cumulative meta-analysis of morning peak expiratory flow in subgroup of the percentage of subjects with symptomatic GERD ≥95%. **C1-2,** Forest plot for morning peak expiratory flow in subgroups of treatment duration ≤12 weeks and >12 weeks. **D1-3,** Forest plot for morning peak expiratory flow in subgroups of different types of proton pump inhibitors (Omeprazole, Lansoprazole, Esomeprazole).

**Supplement 4**

**a.** No publication bias reported in ePEF (P=0.342). Both sensitivity analysis and egger's test further supported the overall results were stable.

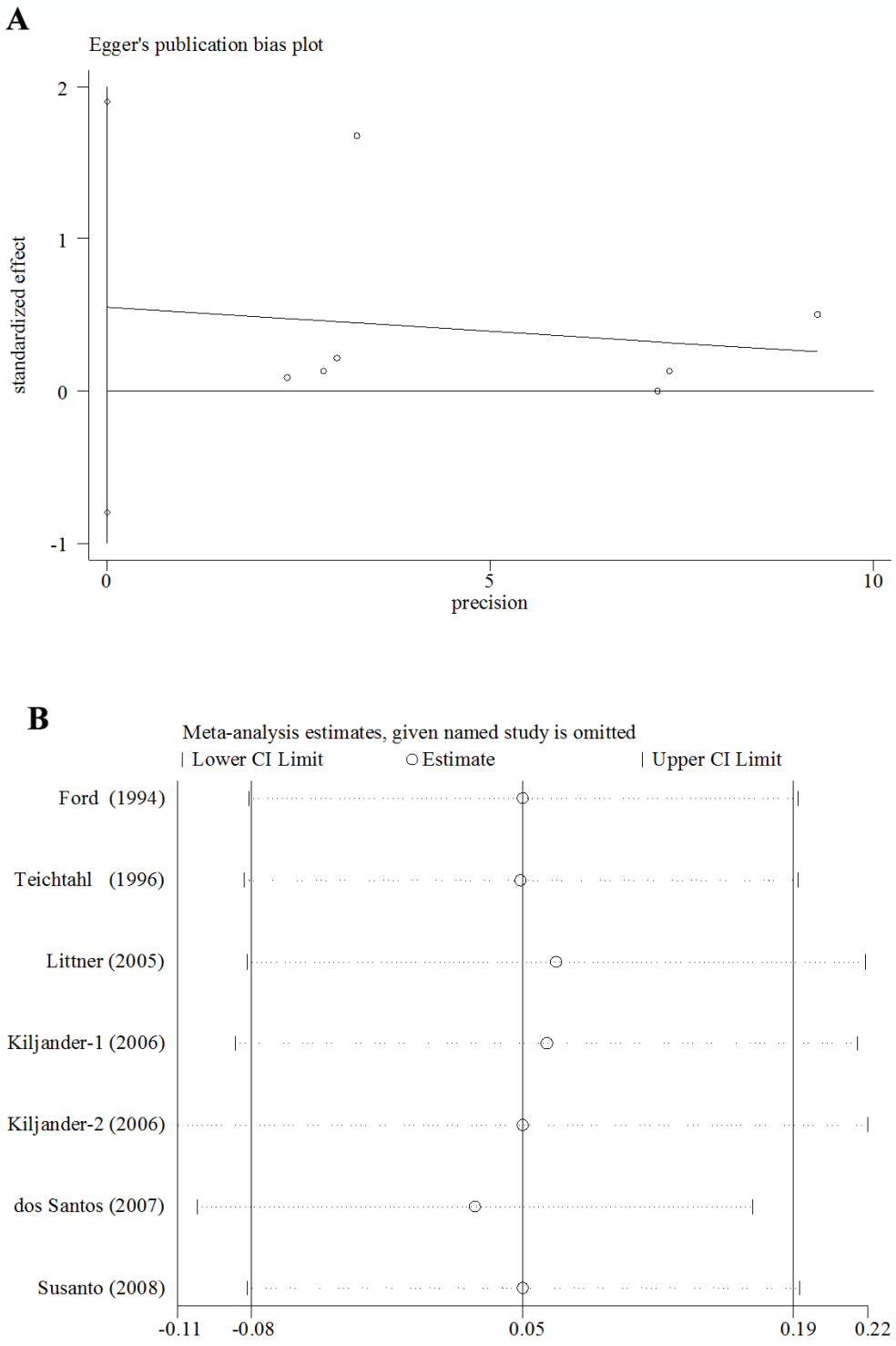
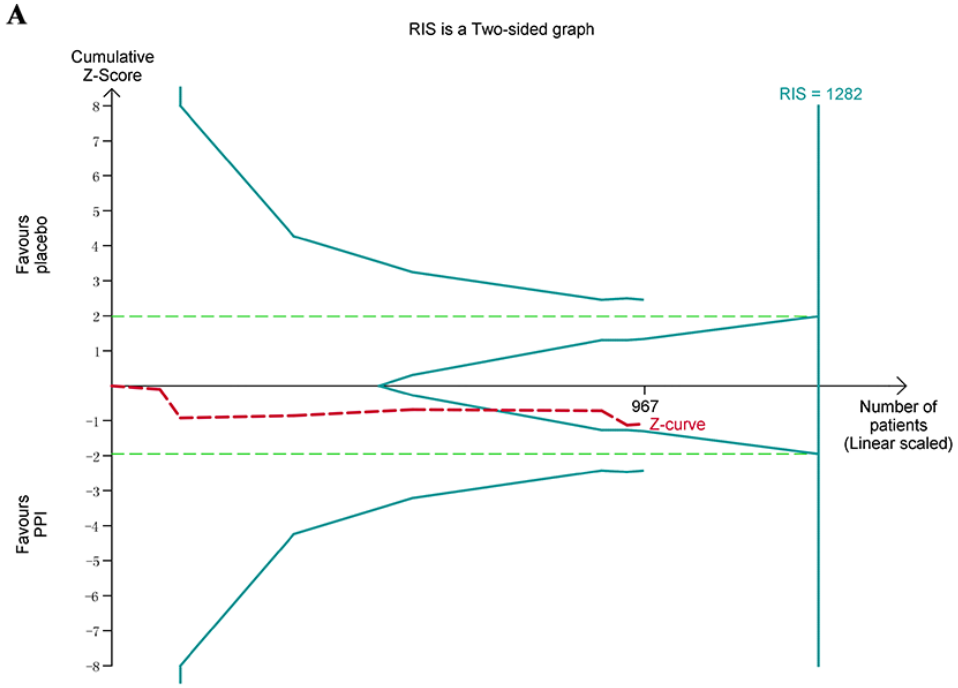



**Figure S3a A,** Egger's publication bias plot for ePEF (P=0.342). **B,** Sensitivity analysis for ePEF.

**b.**

**A**




**B**

| Study or Subgroup | Placebo Mean | SD | Total | Proton Pump Inhibitor Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Ford 1994 | 277 | 78 | 11 | 280 | 81 | 11 | 9.2% | -3.00 [-69.45, 63.45] |
| Littner 2005 | 381 | 97 | 108 | 381 | 82 | 99 | 68.2% | 0.00 [-24.40, 24.40] |
| Susanto 2008 | 280.6 | 71.7 | 16 | 283.7 | 65.9 | 16 | 17.8% | -3.10 [-50.82, 44.62] |
| Teichtahl 1996 | 383 | 155 | 18 | 393 | 124 | 18 | 4.8% | -10.00 [-101.70, 81.70] |
| **Total (95% CI)** | | | **153** | | | **144** | **100.0%** | **-1.31 [-21.46, 18.84]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 3 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)

Mean Difference IV, Random, 95% CI
-100 -50 0 50 100
PPIs better Placebo better

**C**

| Study or Subgroup | Placebo Mean | SD | Total | Proton Pump Inhibitor Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.4.1 Duration ≤12 weeks** | | | | | | | | |
| dos Santos 2007 | 269 | 77 | 22 | 323 | 127 | 22 | 24.9% | -54.00 [-116.06, 8.06] |
| Ford 1994 | 277 | 78 | 11 | 280 | 81 | 11 | 21.7% | -3.00 [-69.45, 63.45] |
| Susanto 2008 | 280.6 | 71.7 | 16 | 283.7 | 65.9 | 16 | 42.1% | -3.10 [-50.82, 44.62] |
| Teichtahl 1996 | 383 | 155 | 18 | 393 | 124 | 18 | 11.4% | -10.00 [-101.70, 81.70] |
| **Subtotal (95% CI)** | | | **67** | | | **67** | **100.0%** | **-16.52 [-47.47, 14.43]** |

Heterogeneity: Tau² = 0.00; Chi² = 1.88, df = 3 (P = 0.60); I² = 0%
Test for overall effect: Z = 1.05 (P = 0.30)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **2.4.2 Duration >12weeks** | | | | | | | | |
| Kiljander-1 2006 | 340.3 | 110.3 | 105 | 342.4 | 127.3 | 111 | 23.5% | -2.10 [-33.82, 29.62] |
| Kiljander-2 2006 | 328.7 | 117 | 171 | 335.2 | 123.3 | 173 | 36.7% | -6.50 [-31.90, 18.90] |
| Littner 2005 | 381 | 97 | 108 | 381 | 82 | 99 | 39.8% | 0.00 [-24.40, 24.40] |
| **Subtotal (95% CI)** | | | **384** | | | **383** | **100.0%** | **-2.88 [-18.27, 12.51]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 2 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)

Mean Difference IV, Random, 95% CI
-100 -50 0 50 100
PPIs better Placebo better

Test for subgroup differences: Chi² = 0.60, df = 1 (P = 0.44), I² = 0%

**D**

| Study or Subgroup | Placebo Mean | SD | Total | Proton Pump Inhibitor Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.3.1 Omeprazole group** | | | | | | | | |
| Ford 1994 | 277 | 78 | 11 | 280 | 81 | 11 | 65.6% | -3.00 [-69.45, 63.45] |
| Teichtahl 1996 | 383 | 155 | 18 | 393 | 124 | 18 | 34.4% | -10.00 [-101.70, 81.70] |
| **Subtotal (95% CI)** | | | **29** | | | **29** | **100.0%** | **-5.41 [-59.22, 48.40]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **2.3.2 Lansoprazole group** | | | | | | | | |
| dos Santos 2007 | 269 | 77 | 22 | 323 | 127 | 22 | 35.5% | -54.00 [-116.06, 8.06] |
| Littner 2005 | 381 | 97 | 108 | 381 | 82 | 99 | 64.5% | 0.00 [-24.40, 24.40] |
| **Subtotal (95% CI)** | | | **130** | | | **121** | **100.0%** | **-19.15 [-69.79, 31.48]** |

Heterogeneity: Tau² = 879.16; Chi² = 2.52, df = 1 (P = 0.11); I² = 60%
Test for overall effect: Z = 0.74 (P = 0.46)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **2.3.3 Esomeprazole group** | | | | | | | | |
| Kiljander-1 2006 | 340.3 | 110.3 | 105 | 342.4 | 127.3 | 111 | 33.3% | -2.10 [-33.82, 29.62] |
| Kiljander-2 2006 | 328.7 | 117 | 171 | 335.2 | 123.3 | 173 | 52.0% | -6.50 [-31.90, 18.90] |
| Susanto 2008 | 280.6 | 71.7 | 16 | 283.7 | 65.9 | 16 | 14.7% | -3.10 [-50.82, 44.62] |
| **Subtotal (95% CI)** | | | **292** | | | **300** | **100.0%** | **-4.53 [-22.84, 13.77]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 2 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.63)

Mean Difference IV, Random, 95% CI
-100 -50 0 50 100
PPIs better Placebo better

Test for subgroup differences: Chi² = 0.28, df = 2 (P = 0.87), I² = 0%

**Figure S3b A,** Trial sequential analysis of evening peak expiratory flow. Heterogeneity adjusted required information size of 1470 subjects calculated in accordance with mean difference of mPEF=20 L/min, "empirical" variance from the meta-analysis of PEF data, α at 0.05, power of 80%, $I^2$ value of 0%. Dashed red cumulative Z curve does not cross solid blue trial sequential monitoring boundaries for benefit or harm, but cross boundaries for futility (blue inner wedge boundaries). Horizontal dotted green lines illustrate traditional level of statistical significance (P=0.05). **B,** Forest plot for evening peak expiratory flow in subgroup of the percentage of subjects with symptomatic GERD ≥95%. **C,** Forest plot for morning peak expiratory flow in subgroups of treatment duration ≤12 weeks and >12 weeks. **D,** Forest plot for evening peak expiratory flow in subgroups of different types of proton pump inhibitors.

**Supplement 5**

No publication reported in $FEV_1$ % predicted (P=0.445). Both sensitivity analysis and egger's test further supported the overall results were stable.

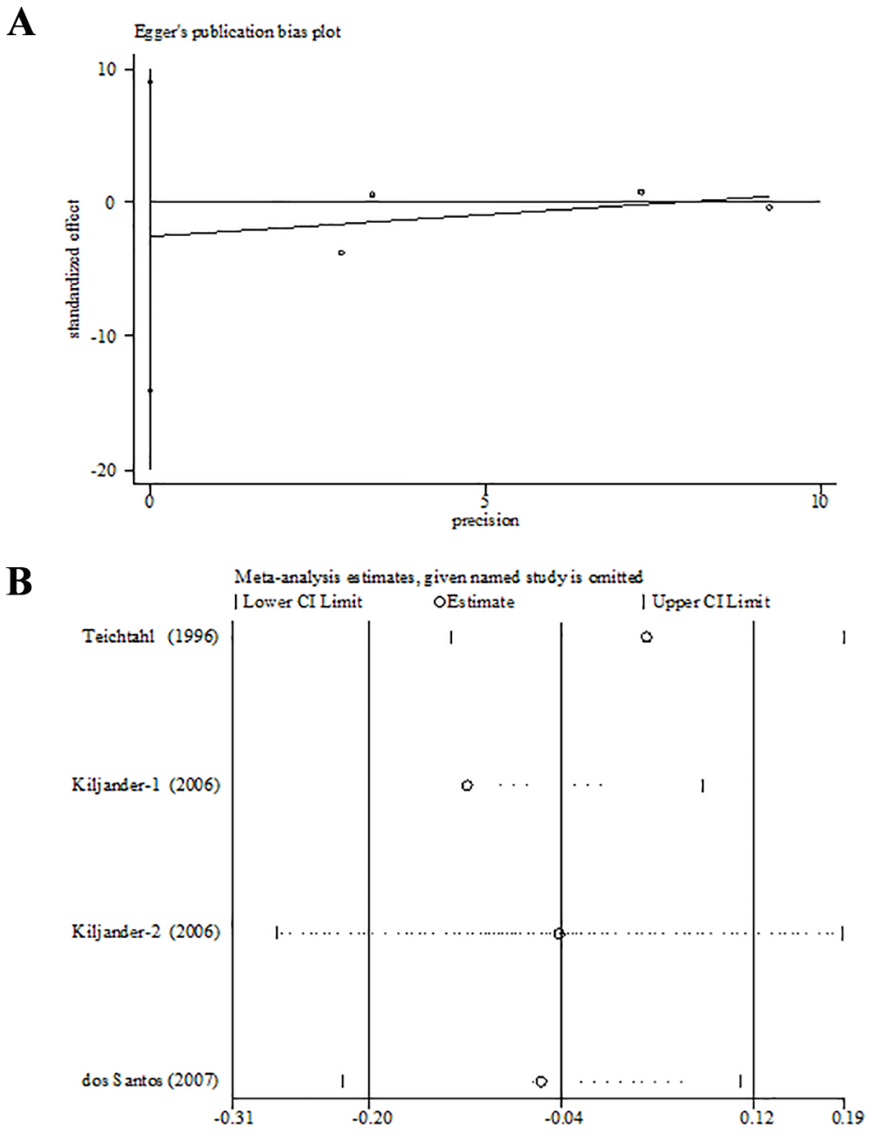



**Figure S4 A,** Egger's publication bias plot for $FEV_1$ % predicted (P=0.445). **B,** Sensitivity analysis for $FEV_1$ % predicted.

**Supplement 6**

No publication reported in asthma symptoms score (P=0.809). Both sensitivity analysis and egger's test further supported the overall results were stable (**supplement 5**).

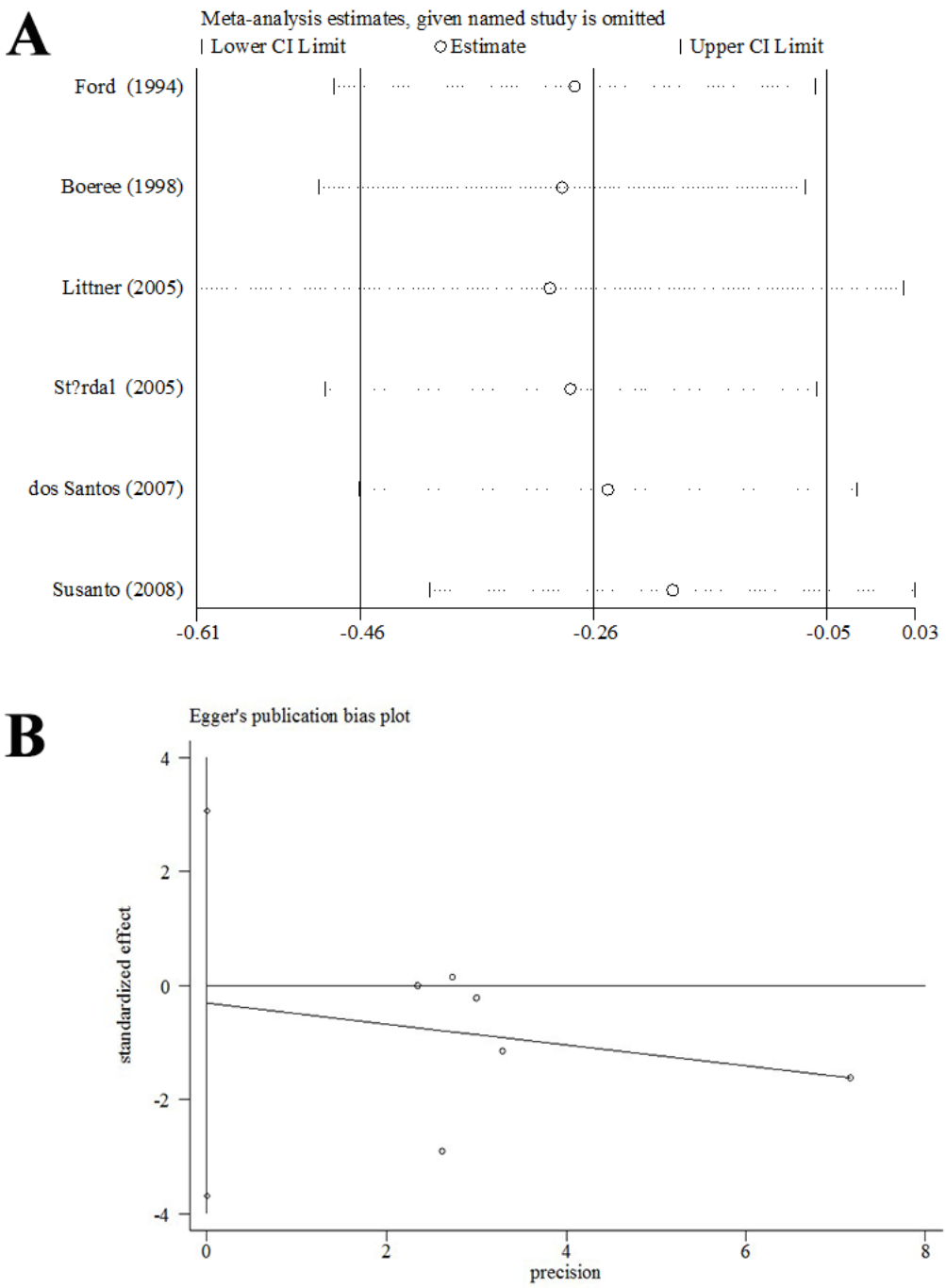



**Figure S5 A,** Egger's publication bias plot for asthma symptoms score (P=0.809). **B,** Sensitivity analysis for asthma symptoms score.

**Supplement 7**

No publication reported in asthma quality of life (P=0.588), but sensitivity analysis showed the results were unstable.

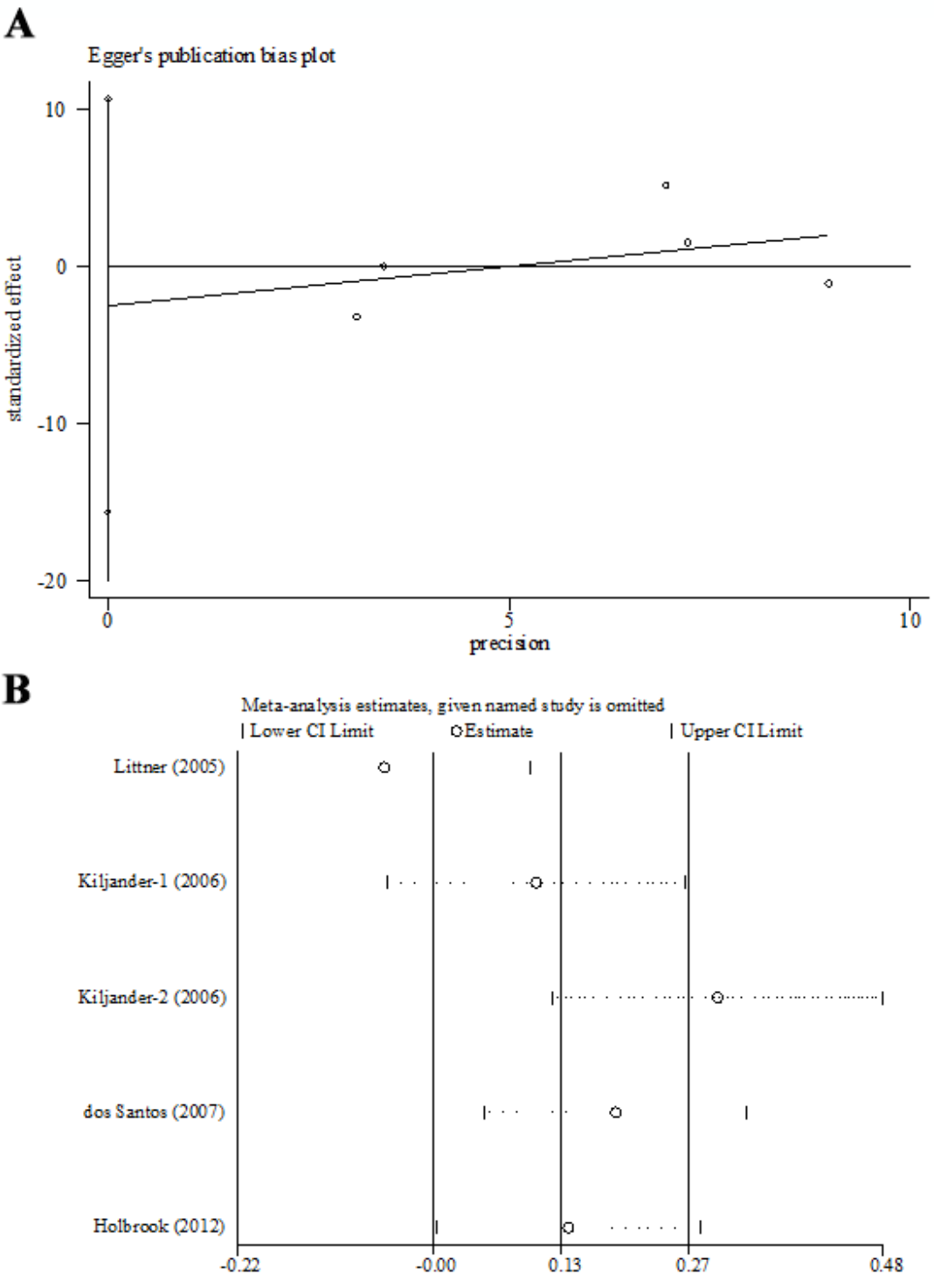



**Figure S6 A,** Egger's publication bias plot for asthma quality of life (P=0.588). **B,** Sensitivity analysis for asthma quality of life.

**Supplement 8**

Cumulative meta-analysis was performed in all the data of secondary outcomes. Except a small positive effect on asthma symptoms score, no significant improvement was found on ePEF and its subgroups analysis, FEV1 % predicted, asthma quality of life and episodes of asthma exacerbation with the application of PPIs.

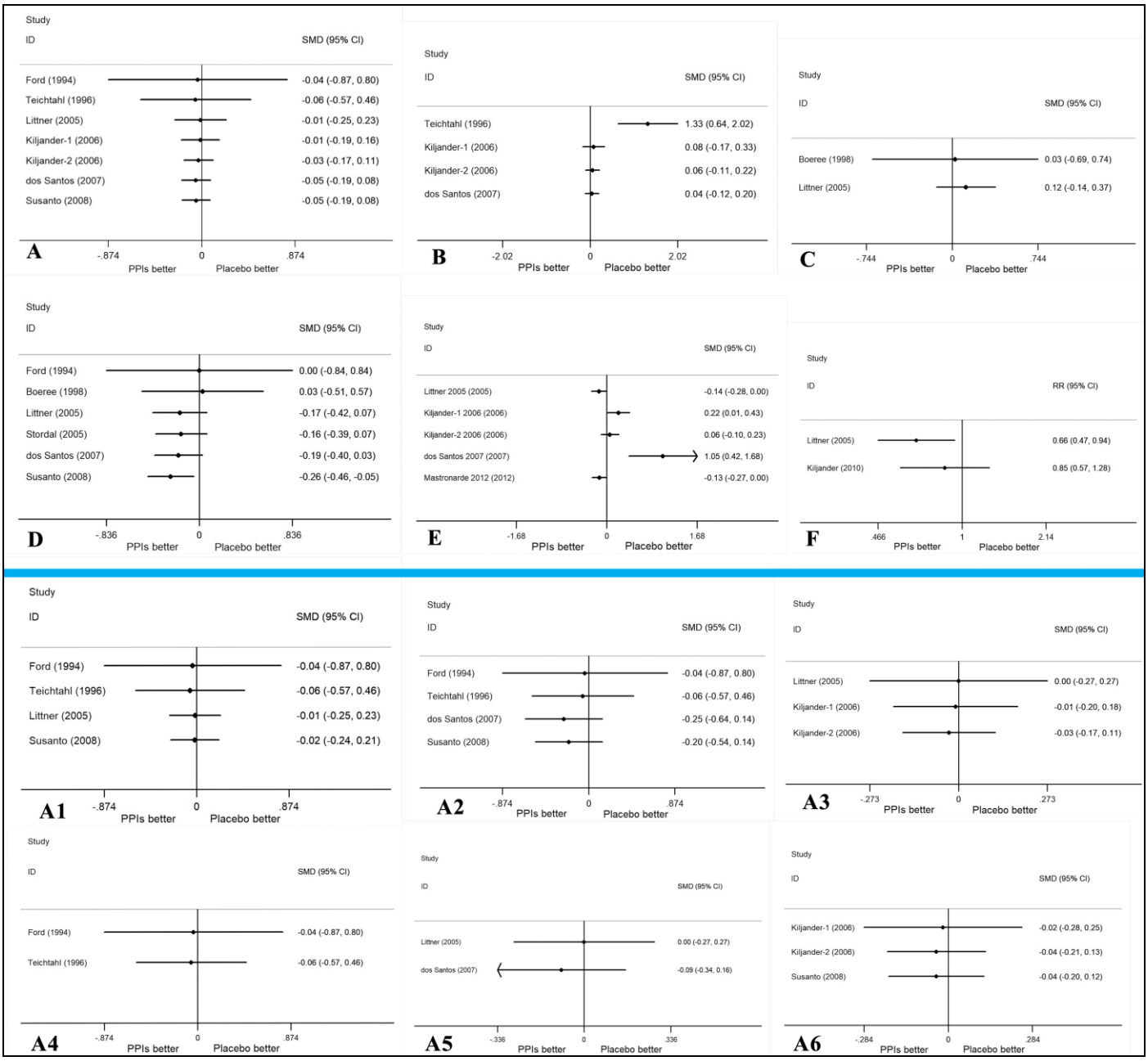



**Figure S7 A**, Cumulative meta-analysis of evening peak expiratory flow. **B,** Cumulative meta-analysis of FEV1 % predicted. **C,** Cumulative meta-analysis of FEV1 (L). **D,** Cumulative meta-analysis of asthma symptoms score. **E,** Cumulative meta-analysis of asthma quality of life score. **F,** Cumulative meta-analysis

of episodes of asthma exacerbation. **A1-6**, Cumulative meta-analysis of evening peak expiratory flow in subgroups of the percentage of subjects with symptomatic GERD ≥95% (**A1**), treatment duration ≤12 weeks (**A2**), treatment duration >12 weeks (**A3**), and different types of proton pump inhibitors (**A4-6**: Omeprazole, Lansoprazole, Esomeprazole).

# PRISMA 2009 Checklist

| 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 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 |
| **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. | 5 |
| 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. | 5-6 |
| 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. | 6, appendix |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 6, appendix |
| 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 |
| 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 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | Appendix |
| 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 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 7 |

# PRISMA 2009 Checklist



| 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). | 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 |
| **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. | 7-8 |
| 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, appendix |
| 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). | 8 |
| 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. | 8-12 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 8-12 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Appendix |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | Appendix |
| **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). | 12-13 |
| 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). | 13 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 13-14 |
| **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. | 14 |

*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(7): e1000097. doi:10.1371/journal.pmed1000097

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