

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 reflux”, “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 "gastroesophageal 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 Reflux or 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 "gastroesophageal reflex"[Title/Abstract]) OR "gastroesophageal reflux"[Title/Abstract]) OR "gastroesophageal reflux disease"[Title/Abstract]) OR "gastroesophageal 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 (gastroesophageal reflux disease)' OR 'gord (gastroesophageal reflux disease)' OR 'cardioesophageal reflux' OR 'cardioesophageal reflux' OR 'esophageal reflux' OR 'esophageal regurgitation' OR 'esophagogastric reflux' OR 'esophagus reflux' OR 'gastric regurgitation' OR 'gastroesophageal reflux' OR 'gastro oesophageal reflux' OR 'gastroesophageal reflex' OR 'gastroesophageal reflux' OR 'gastroesophageal reflux disease' OR 'gastroesophageal regurgitation' OR 'gastroesophagus reflux' OR 'gastroesophageal reflex' OR 'gastroesophageal reflux' OR | 858 |

| | | |
|--|--|--|
| | <p>'gastroesophageal reflux disease' OR 'gastroesophageal regurgitation' OR 'oesophageal reflux' OR 'oesophageal regurgitation' OR 'oesophagogastric reflux' OR 'oesophagus reflux' OR 'reflux, gastroesophageal' OR 'reflux, gastroesophageal' OR 'regurgitation, gastric' OR 'regurgitation, gastroesophageal' OR 'regurgitation, gastroesophageal') 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</p> | |
|--|--|--|

| | |
|---|--|
| <p>'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 'omprany' 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'</p> | |
|---|--|

| | | |
|--|---|--|
| | <p>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'</p> | |
|--|---|--|

| | | |
|----|---|--------|
| | 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 'gastroesophageal reflux':ab,ti OR 'gastroesophageal reflux disease':ab,ti OR 'gastroesophageal 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=("gastroesophageal reflex") OR TS=("gastroesophageal reflux") OR TS=("gastroesophageal reflux disease") OR TS=("gastroesophageal 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 "gastroesophageal reflex" OR "gastroesophageal reflux" OR "gastroesophageal reflux disease" OR "gastroesophageal 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 trial (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.

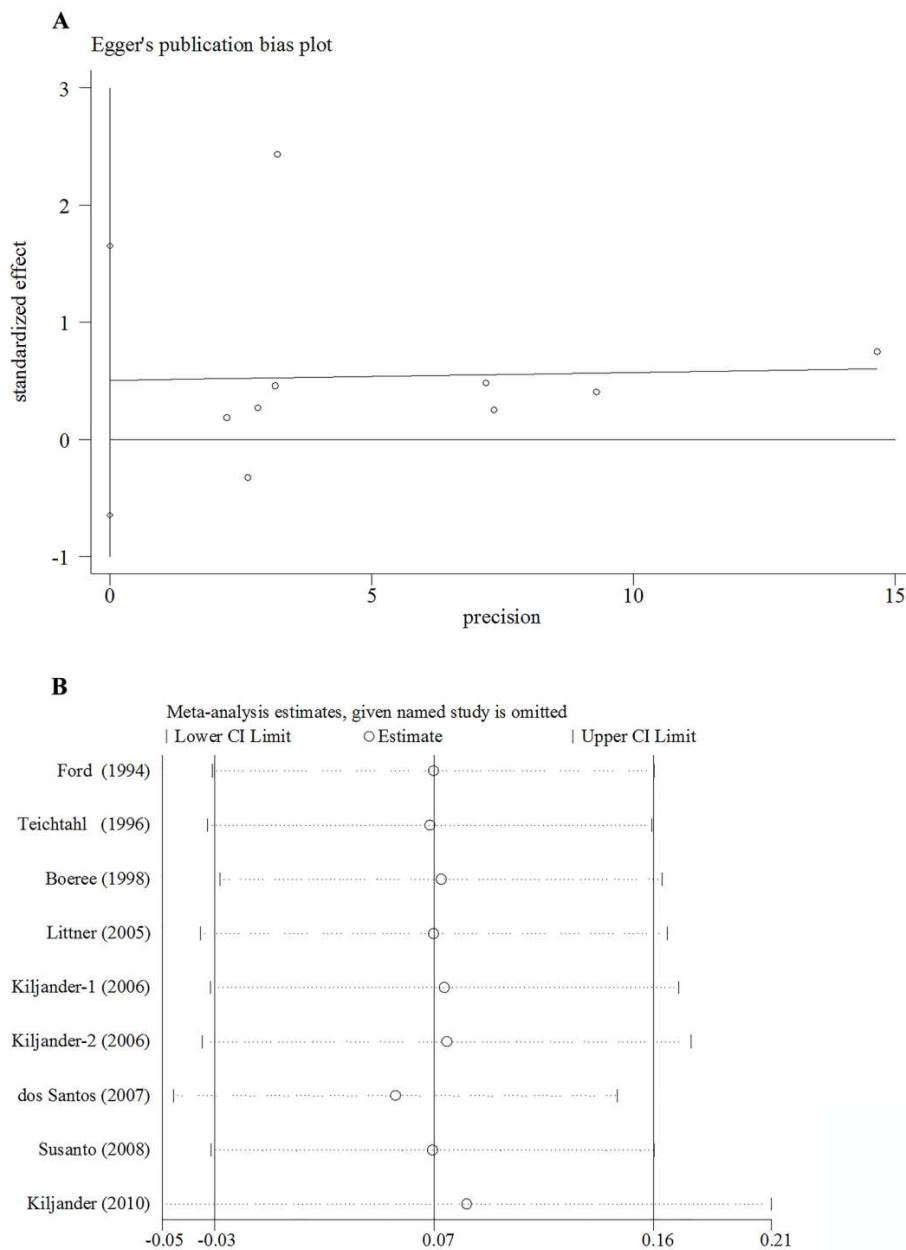


Figure S1 A, Egger's publication bias plot for mPEF ($P=0.336$). **B**, Sensitivity analysis for mPEF.

Supplement 3

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

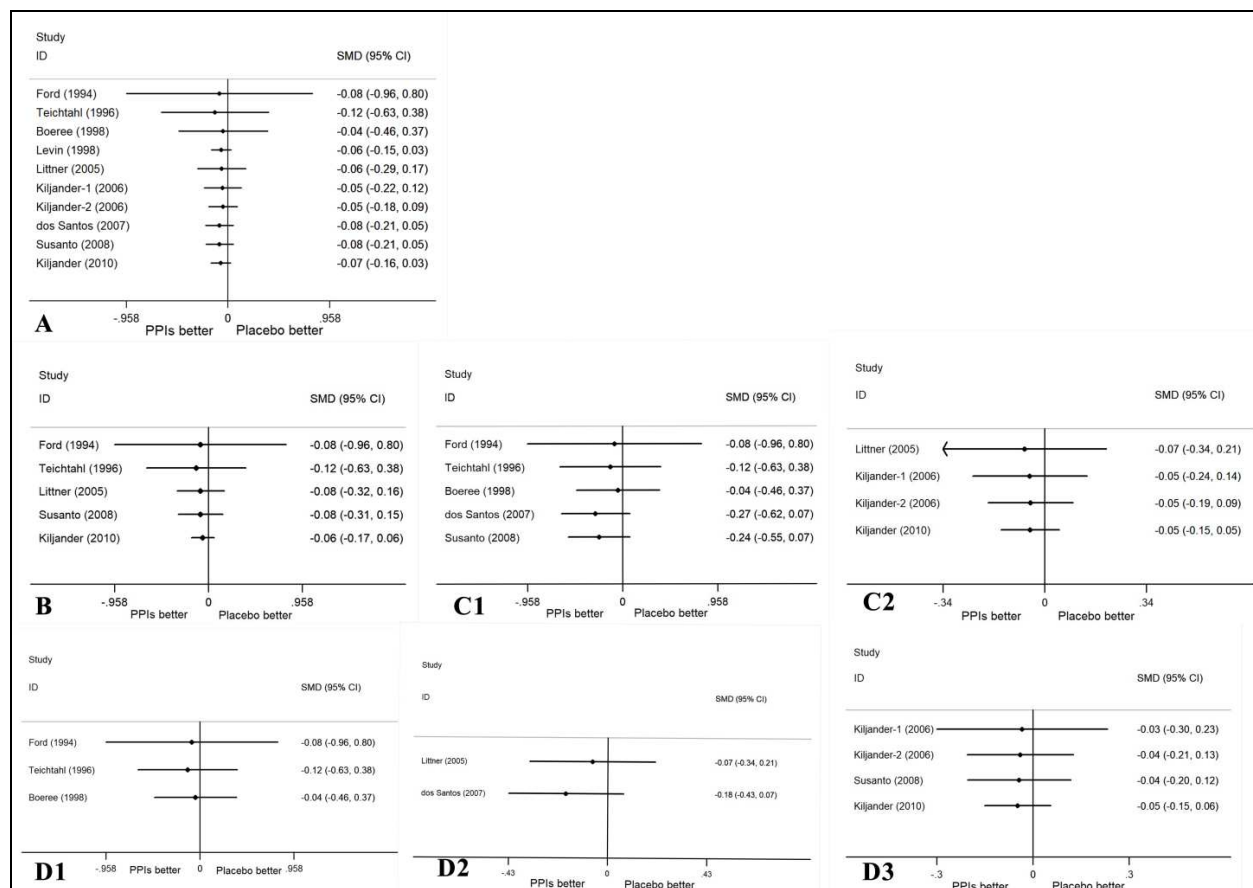


Figure S2 A, Cumulative meta-analysis of morning peak expiratory flow. **B**, Cumulative meta-analysis of morning peak expiratory flow in subgroup of the percentage of subjects with symptomatic GERD $\geq 95\%$. **C1-2**, Forest plot for morning peak expiratory flow in subgroups of treatment duration ≤ 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.

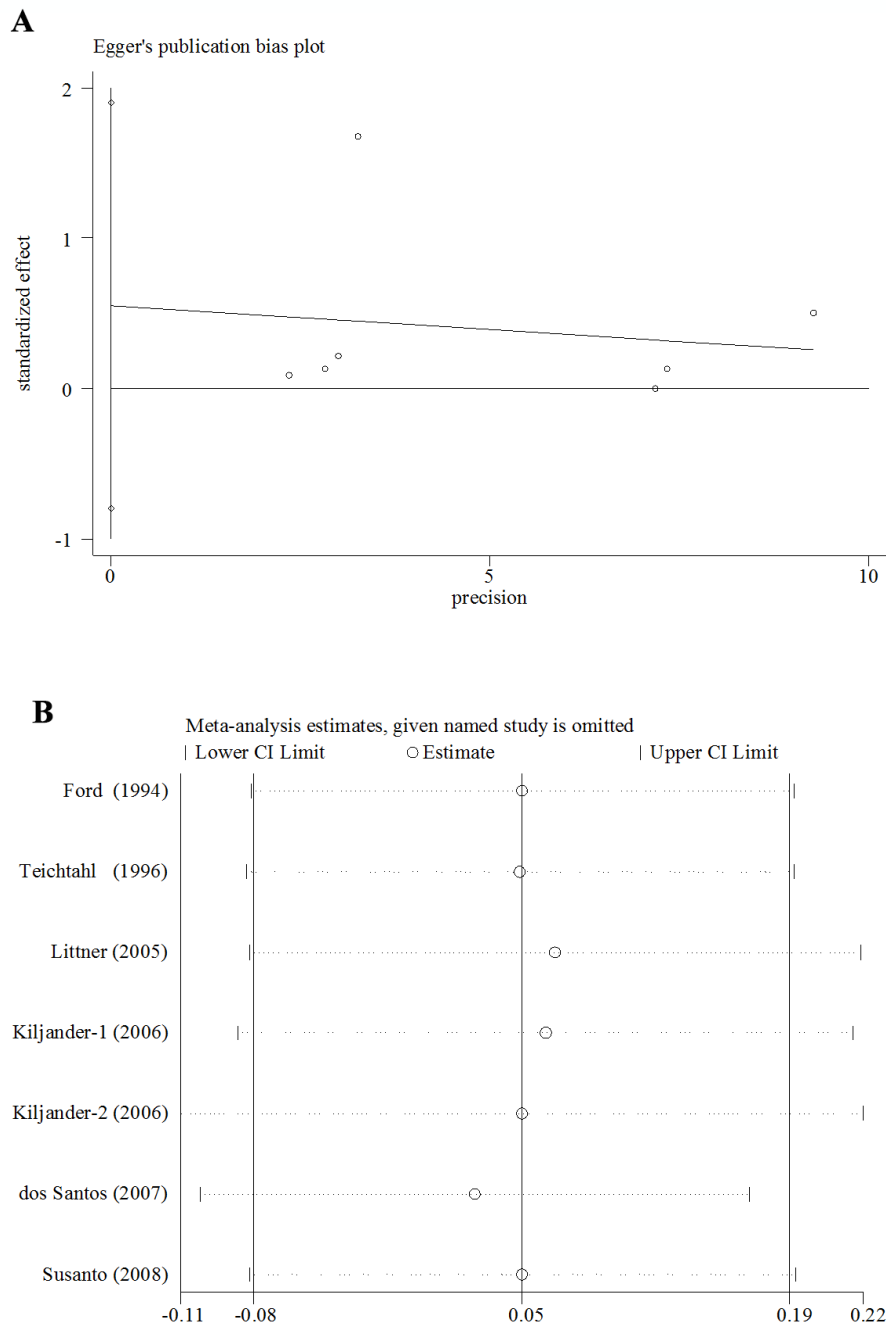


Figure S3a A, Egger's publication bias plot for ePEF ($P=0.342$). **B**, Sensitivity analysis for ePEF.

b.

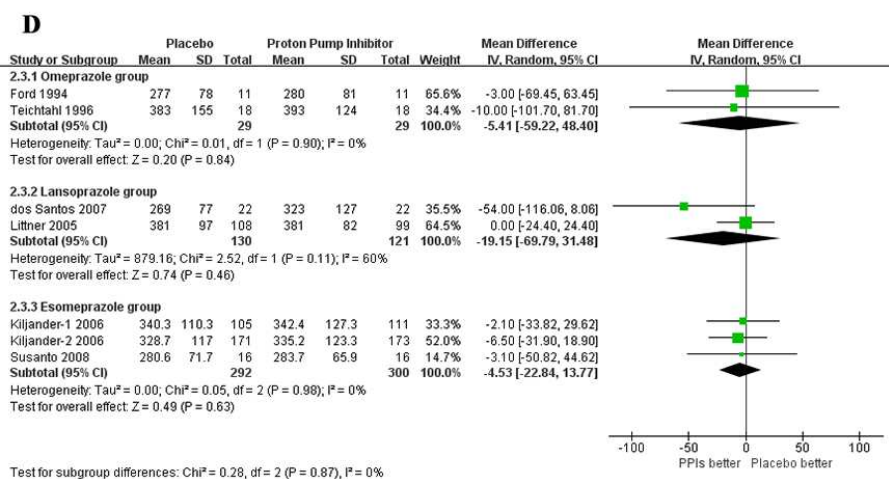
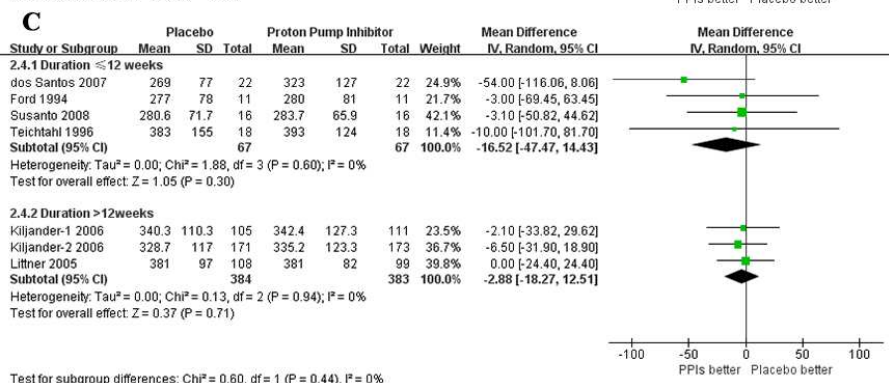
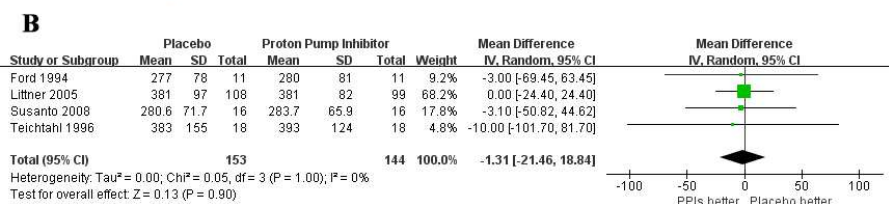
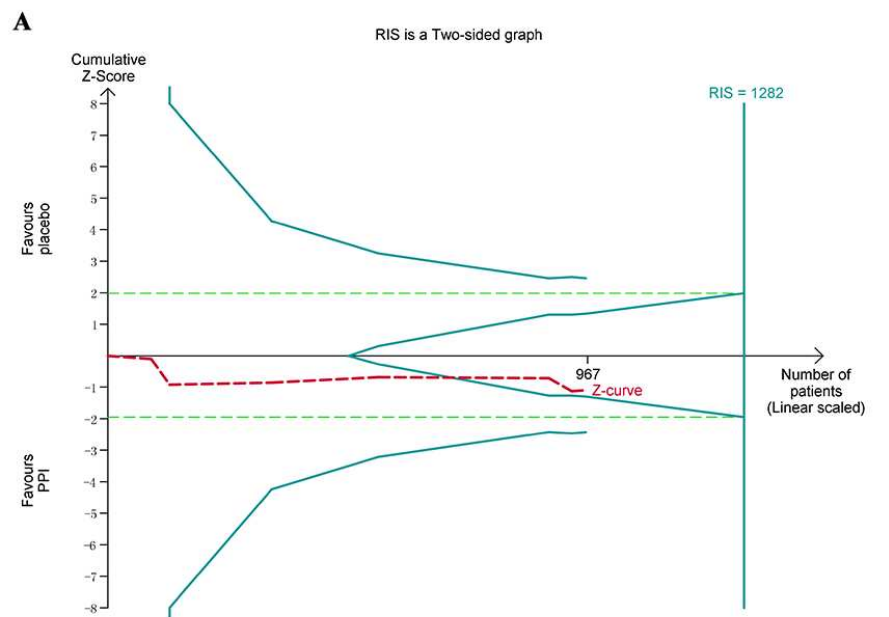


Figure S3b A, Trial sequential analysis of evening peak expiratory flow. Heterogeneity adjusted required information size of 1470 subjects calculated in accordance with mean difference of mPEF=20 L/min, “empirical” variance from the meta-analysis of PEF data, α at 0.05, power of 80%, I^2 value of 0%. 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 $\geq 95\%$. **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 FEV₁ % predicted (P=0.445). Both sensitivity analysis and Egger's test further supported the overall results were stable.

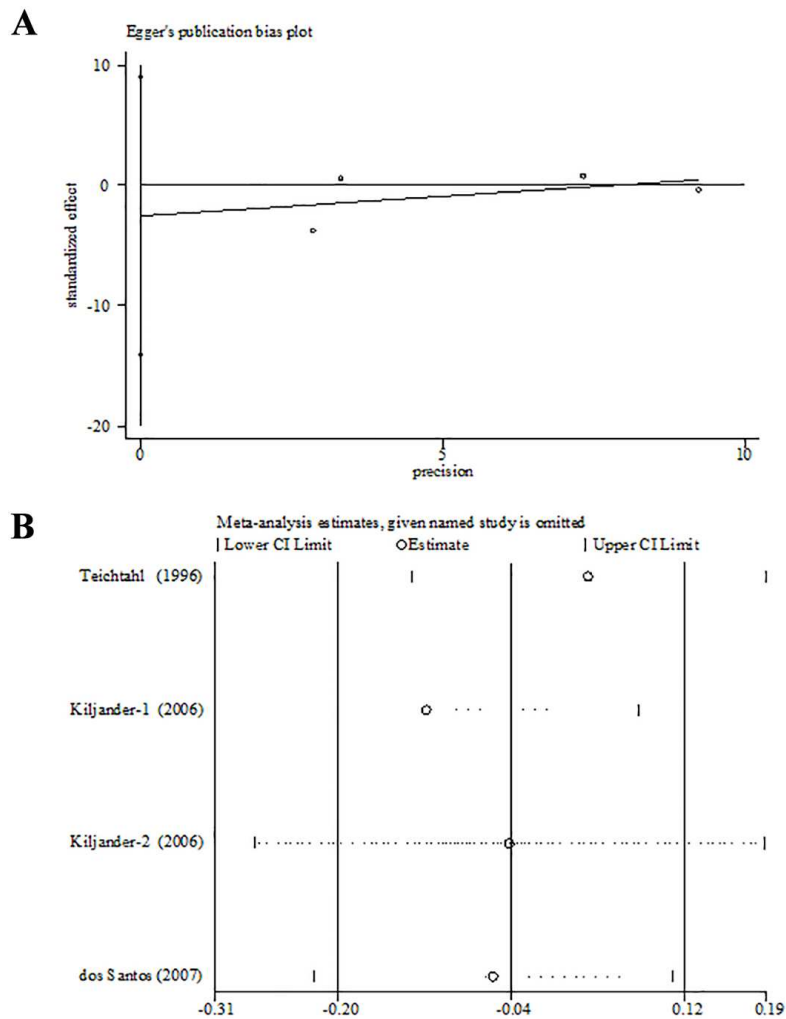


Figure S4 A, Egger's publication bias plot for FEV₁ % predicted (P=0.445). **B**, Sensitivity analysis for FEV₁ % predicted.

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**).

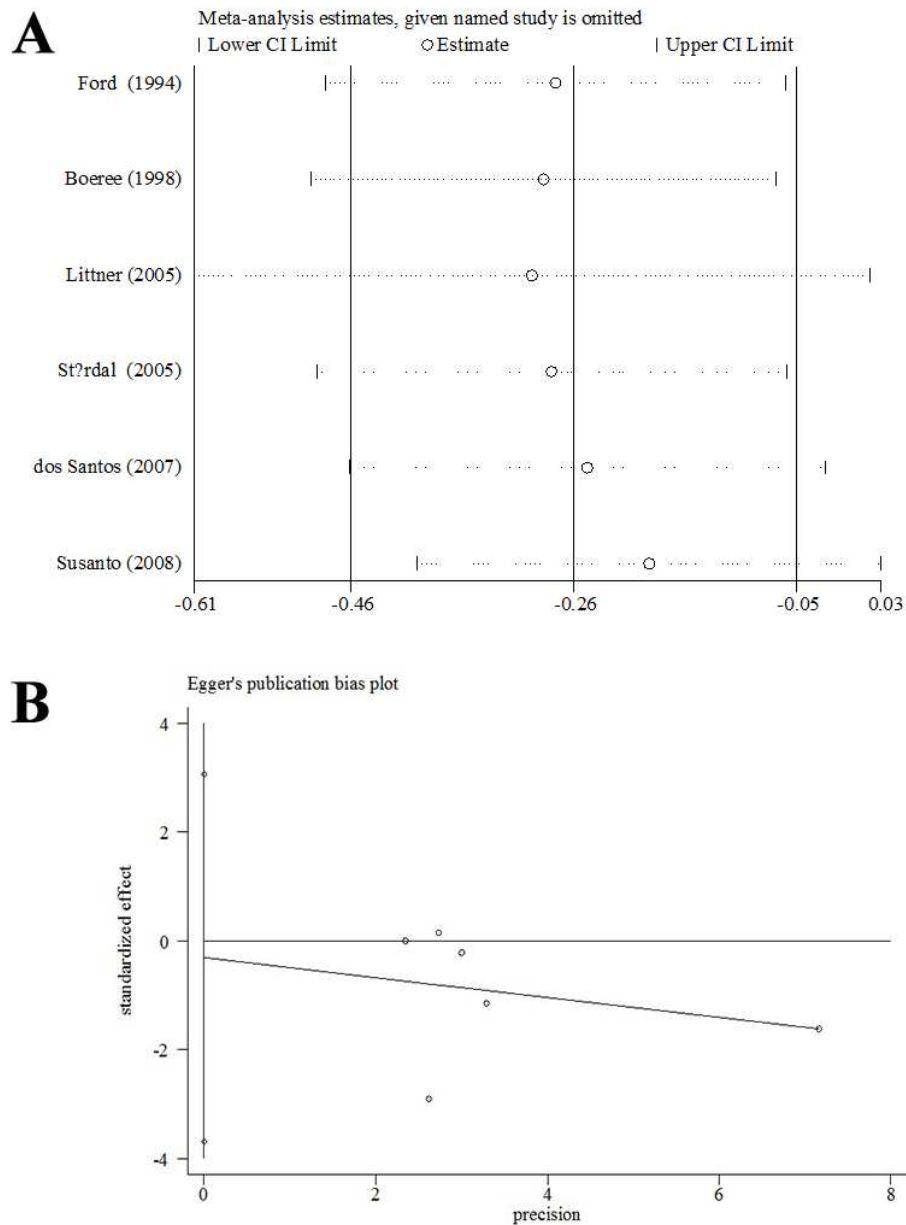


Figure S5 A, Egger's publication bias plot for asthma symptoms score ($P=0.809$). **B**, Sensitivity analysis for asthma symptoms score.

Supplement 7

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

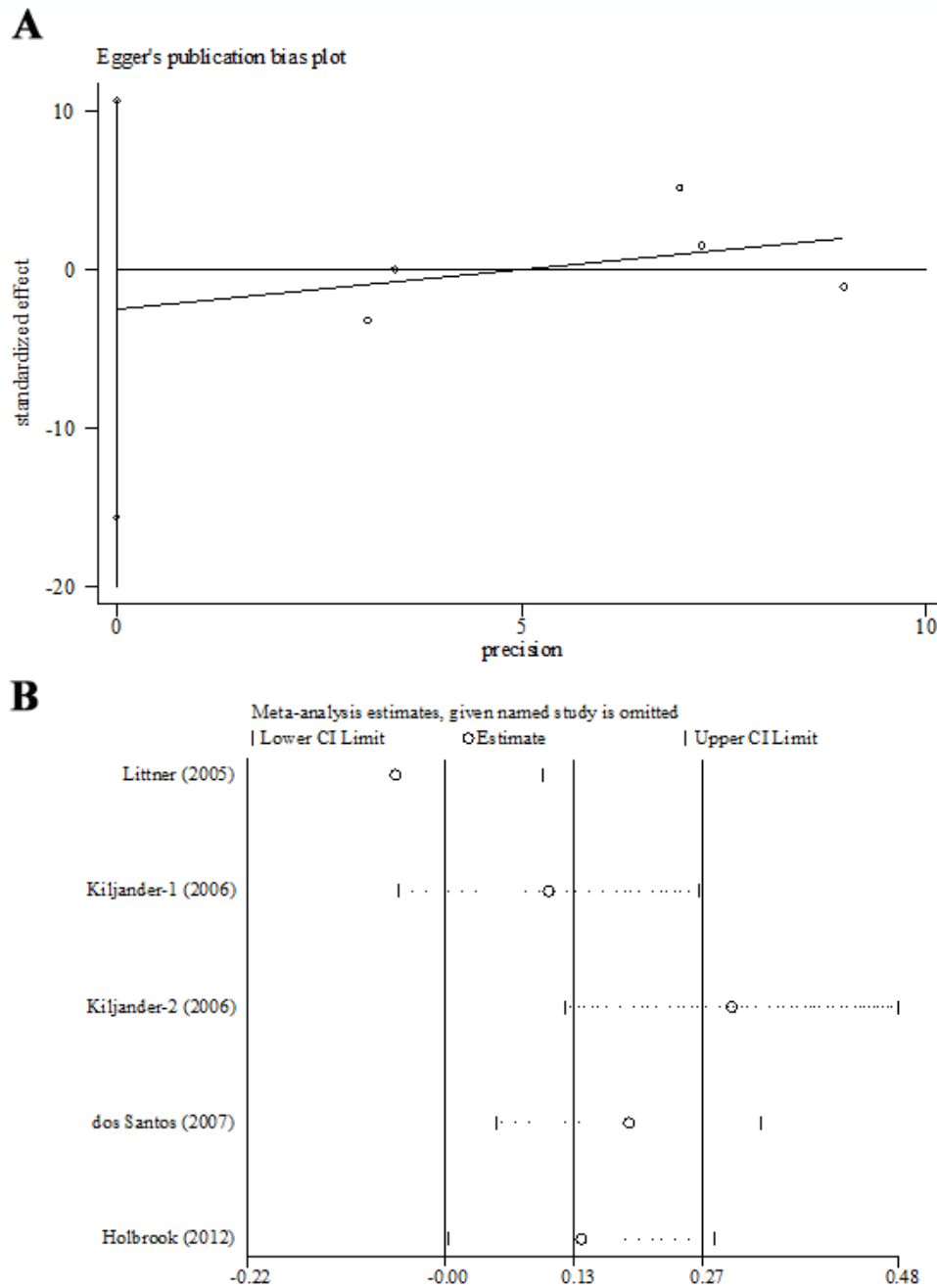


Figure S6 A, Egger's publication bias plot for asthma quality of life ($P=0.588$). **B**, Sensitivity analysis for asthma quality of life.

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.

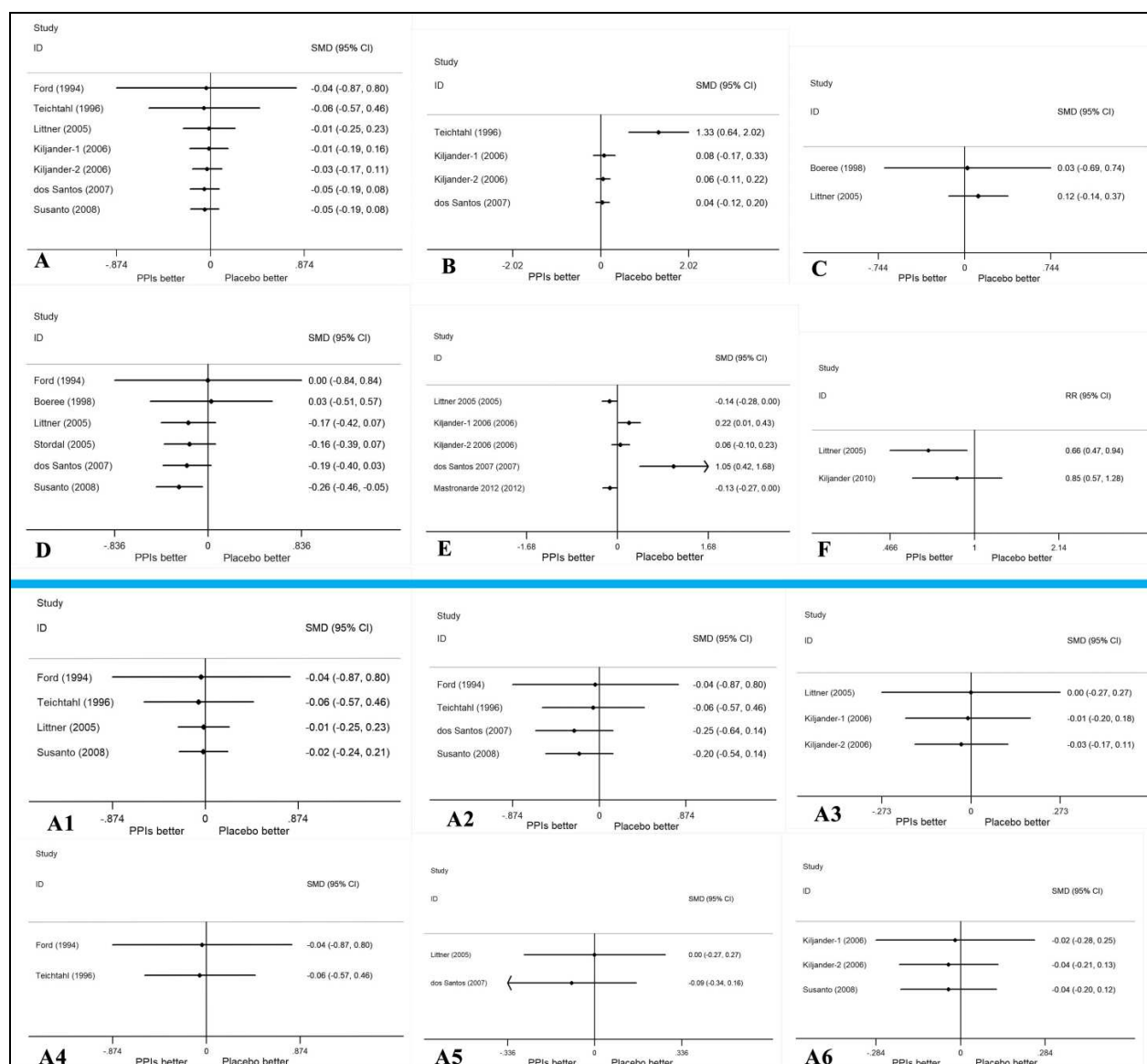


Figure S7 **A**, Cumulative meta-analysis of evening peak expiratory flow. **B**, Cumulative meta-analysis of FEV1 % predicted. **C**, Cumulative meta-analysis of FEV1 (L). **D**, Cumulative meta-analysis of asthma symptoms score. **E**, Cumulative meta-analysis of asthma quality of life score. **F**, 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 $\geq 95\%$ (**A1**), treatment duration ≤ 12 weeks (**A2**), treatment duration > 12 weeks (**A3**), and different types of proton pump inhibitors (**A4-6**: Omeprazole, Lansoprazole, Esomeprazole).