PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Randomized trials of proton pump inhibitors for gastroesophageal reflux disease in patients with asthma: an updated systematic review and meta-analysis
AUTHORS	Zheng, Zhoude; Luo, Yunyun; Li, Jia; Gao, Jinming

VERSION 1 – REVIEW

REVIEWER	Marilena Durazzo University of Turin, Italy
REVIEW RETURNED	16-Nov-2020

GENERAL COMMENTS	"Randomized trials of proton pump inhibitors for gastroesophageal reflux disease in patients with asthma: systematic review and meta-analysis" is an interesting paper. The matter is very innovative and it has been well presented by the Authors. Good work.

REVIEWER	Tianwen Lai Department of Respiratory and Critical Care Medicine, The Affiliated Hospital of Guangdong Medical University
REVIEW RETURNED	30-Nov-2020

GENERAL COMMENTS	The manuscript by Zheng et al trying to explore whether PPIs improved morning peak expiratory flow (mPEF) in asthma patients with GERD using Meta-analysis. The paper is carefully evaluated by me and I have got following criticisms: 1. This is not the first meta-analysis to explore the application of PPI in asthmatic patients with esophageal reflux disease. The five outcome indicators were the same with the previous study (Arch Intern Med. 2011;171:620-629). Moreover, the conclusions of this meta-analysis are almost the same with the previous study. Thus, this paper is a updated Meta-analysis. 2. Why not included the study by Peterson KA2009? 3. In terms of morning PEF, Walter W. Chan 2011 believes that the application of PPI can have a small, statistically significant improvement in morning PEF rate (8.68 L/min; [95% CI, 2.35-15.02]; P=.007). This article believes that there is no effect (8.68 L/min, 95% CI [-2.35, 19.37], P=0.11). However, based on the selected methodology, Walter W. Chan 2011 chose a cumulative meta-analysis, using the calibrated effect size of the literature as the analysis data Mean Change vs Placebo (95% CI), and the original data mean was selected in this article ±SD is used as raw data. Raw data like this article will cause calibration errors. Therefore, the conclusion of this article needs to be studied. 4. Why Levin 1998 (omeprazole) and mastronarde 2009 (esomeprazole) cannot be included in morning PEF analysis? 5. It is recommended that the author use the effect value to do a cumulative meta-analysis of all the data in the Stata software, and

	then see how the conclusion is.

REVIEWER	Iosief Abraha Servizio Immunostrasfusionale, USL Umbria 2, Foligno, Italy
REVIEW RETURNED	16-Apr-2021

GENERAL COMMENTS	1) Usually in the meta-analysis graph the intervention group is placed in the left side while the control group in right side. Please amend the figures accordingly. 2) Page 9, line 54: the Authors report “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] ….”. However, I see only one study (Dos Santos 2007) showing improvement from Figure 3A. Please amend the text accordingly. 3) Page 6, line 45. Authors report: “This review was restricted to studies with treatment duration of 4 weeks and above”. Please indicate in the Results whether there were studies with duration less than 4 weeks. If studies were present please discuss whether this might affect the results of the review. 4) Page 10. Subgroup analysis should be written in a better way. I suggest to split the period in separate paragraphs. Please add consistently number of studies and number of population for each of the subgroup analysis. 5) Pages 11-12. Please add number of participants as necessary. Figure citation should be placed after heterogeneity description 6) The risk of selectively reporting bias looks like unclear only in one study. However, since authors underlined the fact that some data and/or relevant outcomes were not reported or available this particular item of the risk of bias should be revised.

VERSION 1 – AUTHOR RESPONSE

Responses to the comments of Reviewer: 1

Comment 1: "Randomized trials of proton pump inhibitors for gastroesophageal reflux disease in patients with asthma: systematic review and meta-analysis" is an interesting paper. The matter is very innovative and it has been well presented by the Authors. Good work.

Reply:

Thank you very much for your careful review of our manuscript. We greatly appreciate your affirmation of our study.

Responses to the comments of Reviewer: 2

Comment 1: This is not the first meta-analysis to explore the application of PPI in asthmatic patients with esophageal reflux disease. The five outcome indicators were the same with the previous study (Arch Intern Med. 2011;171:620-629). Moreover, the conclusions of this meta-analysis are almost the same with the previous study. Thus, this paper is a updated Meta-analysis.

Reply:

Thank you very much for your comment. We agree with the reviewer that this study is an updated Meta-analysis. Compared with the previous study, our review included a larger number of participants

(1886 participants VS 1004 participants) and have adopted Trial sequential analysis and cumulative meta-analysis to further confirm the overall effect. In terms of the manuscript, we have corrected this error in the **Title** (Page 2: line 4) and in '**Strengths and limitations of this study**' section (Page 4: line5-9).

<Original version>

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

<Revised version>

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

<Original version>

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.

<Revised version>

Strengths and limitations of this study: This systematic review strictly followed the methodology recommendations of the Cochrane Handbook, together with a comprehensive literature search.

Comment 2: Why not included the study by Peterson KA2009?

Reply:

We sincerely thank you for your careful review of our paper. We thoroughly reread this article (Peterson KA, Dig Dis Sci, 2009). The reasons why we excluded this study are as follow:

According to the GINA 2021, making the diagnosis of asthma is on the basis of the history of variable respiratory symptoms, variable expiratory airflow limitation and lung function. However, Peterson and his colleagues did not perform serial pulmonary function tests for the included participants. Thus, they selected the participants with "exercise-triggered asthma" (ETA), which cannot be regarded as chronic asthma.

With the careful consideration, the population of ETA unable to meet the inclusion criteria of our study. Thus, we excluded the study by Peterson KA2009.

Comment 3: In terms of morning PEF, Walter W. Chan 2011 believes that the application of PPI can have a small, statistically significant improvement in morning PEF rate (8.68 L/min; [95% CI, 2.35-15.02]; P=.007). This article believes that there is no effect (8.68 L/min, 95% CI [-2.35, 19.37], P=0.11). However, based on the selected methodology, Walter W. Chan 2011 chose a cumulative meta-analysis, using the calibrated effect size of the literature as the analysis data Mean Change vs Placebo (95% CI), and the original data mean was selected in this article ±SD is used as raw data.

Raw data like this article will cause calibration errors. Therefore, the conclusion of this article needs to be studied.

Reply:

Thank you very much for your comment. We agree that raw data from the original studies may cause calibration errors. In order to further confirmed this conclusion, we adopted a cumulative meta-analysis in morning PEF rate, and the results remained no significant improvement (SMD 0.07, 95% CI [-0.03, 0.16]) (revised versions are detailed in "**comment 5**"), which was in agreement with the results of trial sequential analysis.

In our study, we included 1914 participants compared with 1004 patients in the Chan's study. Cumulative meta-analysis and trial sequential analysis were conducted in morning PEF rate, showing consistent results that the use of PPIs likely had no significant improvement on morning PEF rate.

Comment 4: Why Levin 1998 (omeprazole) and mastronarde 2009 (esomeprazole) cannot be included in morning PEF analysis?

Reply:

We sincerely thank the reviewer for this comment. Both studies did not show the adaptable data (mean and ±SD) of morning PEF rate. We have tried to contact the authors of both studies for the raw data, but did not get any response.

Although the study of Levin 1998 showed a statistically significant positive effect in morning PEF rate, there were only 28 participants included in this study, which seems unlikely to change the overall effect of this outcome of the current study.

As for Mastronarde 2009 (esomeprazole), in fact, this study found that no significant effect in morning PEF rate with the application of PPIs (data not published), which indicates that whether or not included this study is unlikely to alter the results of no improvement in our review. We have tried to contact the author but did not get reply.

Thus, we are unable to include both of studies in morning PEF analysis

Comment 5: It is recommended that the author use the effect value to do a cumulative meta-analysis of all the data in the Stata software, and then see how the conclusion is.

Reply:

We greatly appreciate the reviewer for this constructive comment. We have conducted a cumulative meta-analysis of all the outcomes in the Stata software. We have added related statement into **Method** (Page 8: line 37), **Results** (Page 11: line 8-12， page 12: line 58) and **Discussion** part (Page 13: line 30-31) in our revised manuscript and added results of cumulative meta-analysis into **Appendix** (**Supplementary 3, 8**):

<Original version>

Method: We conducted sensitivity analysis and Egger's test to identify data stability and publication bias, respectively (StataSE 12.0).

<Revised version>

Method: 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).

<Revised version>

Results (Page 11: line 8-12): 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**).

Results (page 12: line 58): 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, FEV1 % predicted, asthma quality of life and episodes of asthma exacerbation with the application of PPIs (**Figure S7**).

Discussion (Page 13: line 30-31): These results were further confirmed by the application of TSA and cumulative meta-analysis.

Appendix:

Supplement 3 (Page 46)

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

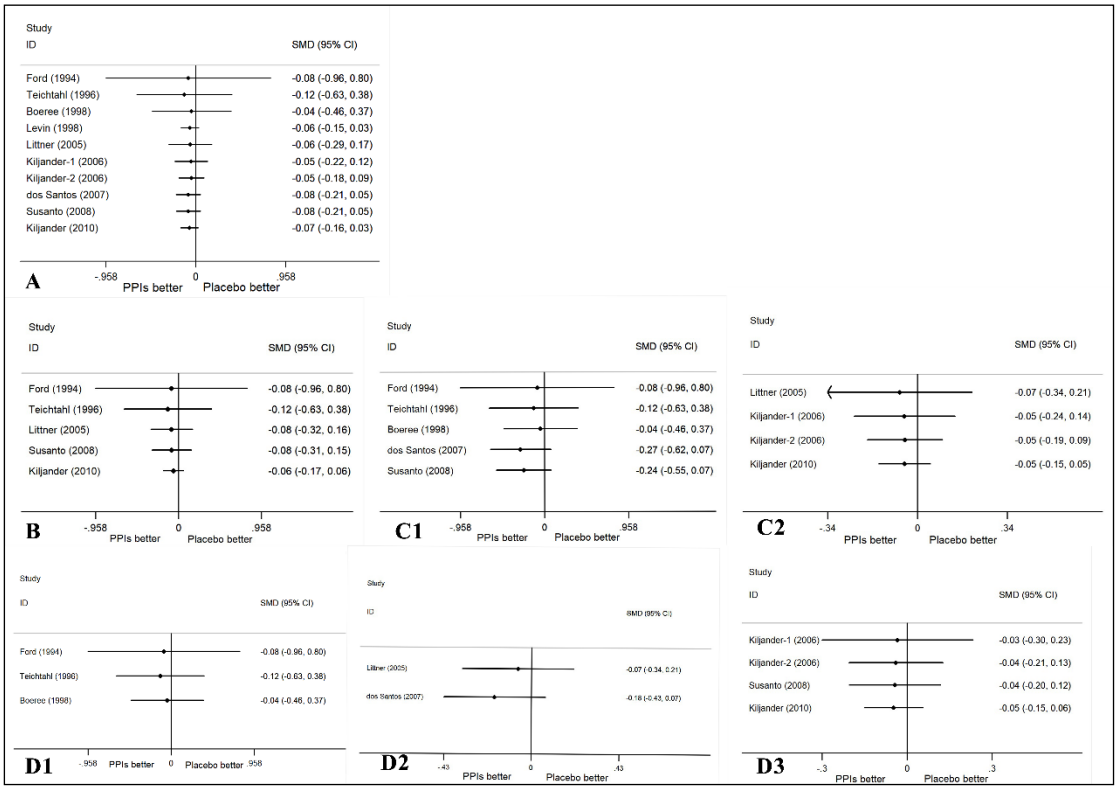


Figure S2 A, Cumulative meta-analysis of morning peak expiratory flow. **B**, Cumulative meta-analysis of morning peak expiratory flow in subgroup of the percentage of subjects with symptomatic GERD ≥95%. **C1-2**, Forest plot for morning peak expiratory flow in subgroups of treatment duration ≤12

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 8 (Page 53)

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.

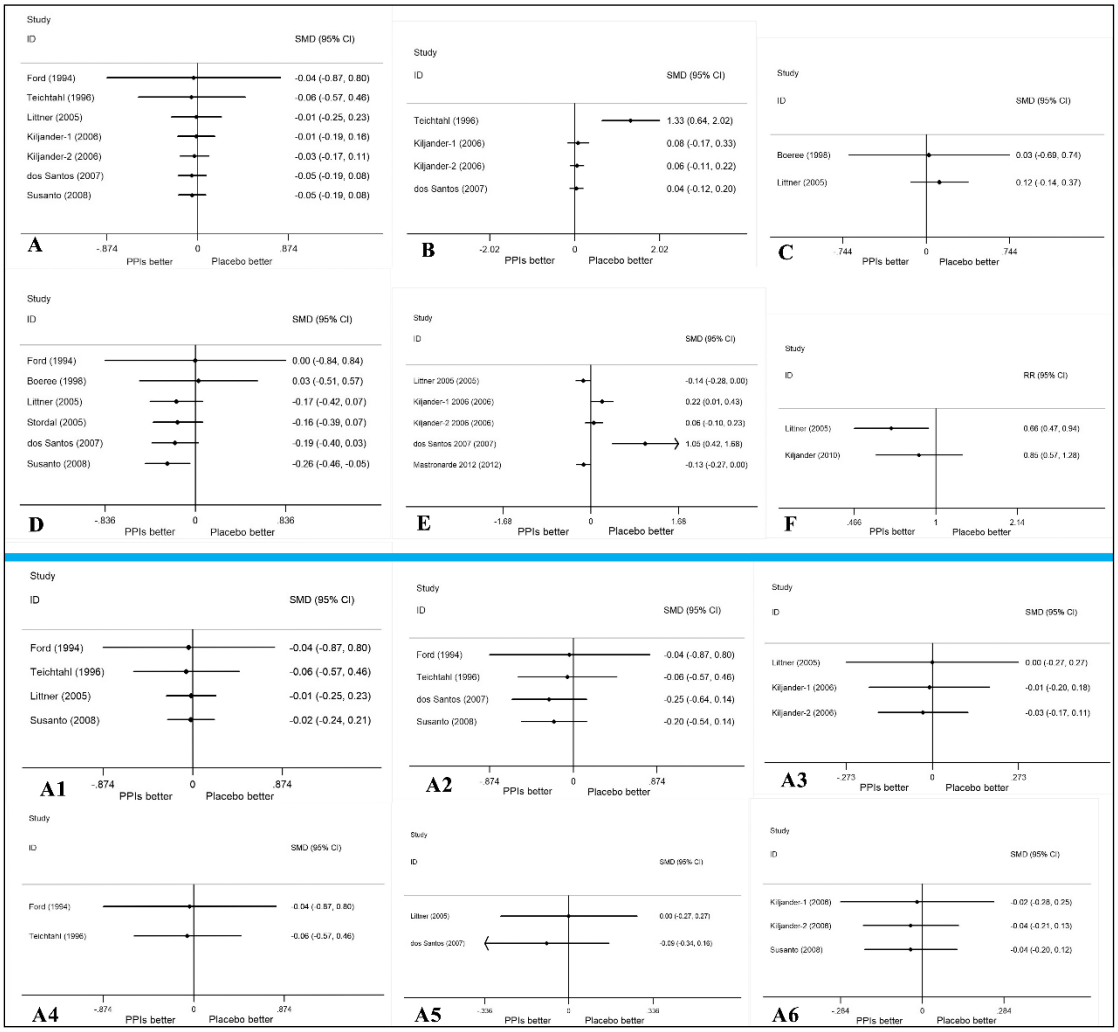


Figure S7 A, Cumulative meta-analysis of evening peak expiratory flow. **B,** Cumulative meta-analysis of FEV1 % predicted. **C,** Cumulative meta-analysis of FEV1 (L). **D,** Cumulative meta-analysis of asthma symptoms score. **E,** Cumulative meta-analysis of asthma quality of life score. F, Cumulative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

Responses to the comments of Reviewer: 3

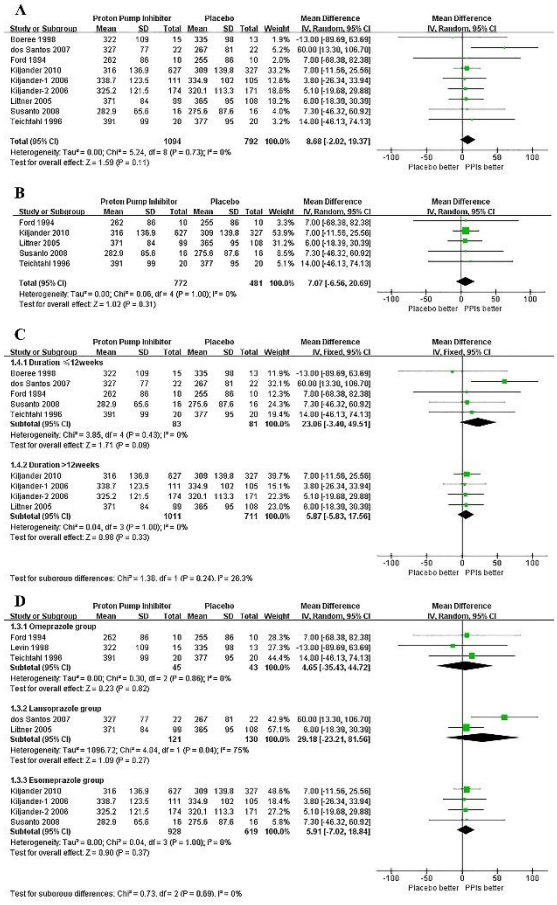
Comment 1: Usually in the meta-analysis graph the intervention group is placed in the left side while the control group in right side. Please amend the figures accordingly.

Reply:

Thank you very much for your careful review of our paper. We agree with the reviewer and have corrected this error in all the meta-analysis graphs in the following **Figures** (Page 26, 28) and the **Appendix** (**Figure S3b**, page 48).

<Original version>

Figure 3:



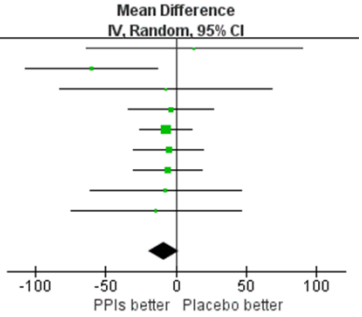
<Revised version>

Figure 3:

A

Study or Subgroup	Placebo Mean	Placebo SD	Placebo Total	Proton Pump Inhibitor Mean	Proton Pump Inhibitor SD	Proton Pump Inhibitor Total	Weight	Mean Difference IV, Random, 95% CI
Boeree 1998	335	98	13	322	109	15	1.9%	13.00 [-63.69, 89.69]
dos Santos 2007	267	81	22	327	77	22	5.2%	-60.00 [-106.70, -13.30]
Ford 1994	255	86	10	262	86	10	2.0%	-7.00 [-82.38, 68.38]
Kiljander-1 2006	334.9	102	105	338.7	123.5	111	12.6%	-3.80 [-33.94, 26.34]
Kiljander 2010	309	139.8	327	316	136.9	627	33.2%	-7.00 [-25.56, 11.56]
Kiljander-2 2006	320.1	113.3	171	325.2	121.5	174	18.6%	-5.10 [-29.88, 19.68]
Littner 2005	365	95	108	371	84	99	19.2%	-6.00 [-30.39, 18.39]
Susanto 2008	275.6	87.6	16	282.9	65.6	16	4.0%	-7.30 [-60.92, 46.32]
Teichtahl 1996	377	95	20	391	99	20	3.2%	-14.00 [-74.13, 46.13]
Total (95% CI)			**792**			**1094**	**100.0%**	**-8.68 [-19.37, 2.02]**

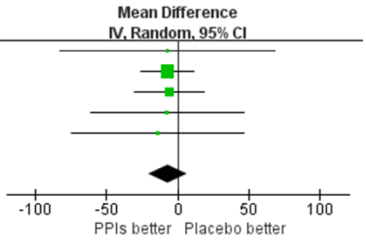
Heterogeneity: Tau² = 0.00; Chi² = 5.24, df = 8 (P = 0.73); I² = 0%
Test for overall effect: Z = 1.59 (P = 0.11)



B

Study or Subgroup	Placebo Mean	Placebo SD	Placebo Total	Proton Pump Inhibitor Mean	Proton Pump Inhibitor SD	Proton Pump Inhibitor Total	Weight	Mean Difference IV, Random, 95% CI
Ford 1994	255	86	10	262	86	10	3.3%	-7.00 [-82.38, 68.38]
Kiljander 2010	309	139.8	327	316	136.9	627	53.9%	-7.00 [-25.56, 11.56]
Littner 2005	365	95	108	371	84	99	31.2%	-6.00 [-30.39, 18.39]
Susanto 2008	275.6	87.6	16	282.9	65.6	16	6.5%	-7.30 [-60.92, 46.32]
Teichtahl 1996	377	95	20	391	99	20	5.1%	-14.00 [-74.13, 46.13]
Total (95% CI)			**481**			**772**	**100.0%**	**-7.07 [-20.69, 6.56]**

Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 4 (P = 1.00); I² = 0%
Test for overall effect: Z = 1.02 (P = 0.31)



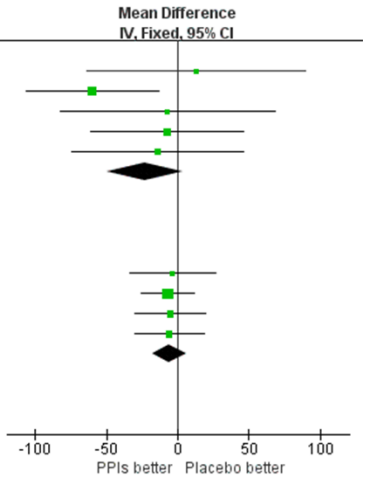
C

Study or Subgroup	Placebo Mean	Placebo SD	Placebo Total	Proton Pump Inhibitor Mean	Proton Pump Inhibitor SD	Proton Pump Inhibitor Total	Weight	Mean Difference IV, Fixed, 95% CI
1.4.1 Duration ≤12weeks								
Boeree 1998	335	98	13	322	109	15	11.9%	13.00 [-63.69, 89.69]
dos Santos 2007	267	81	22	327	77	22	32.1%	-60.00 [-106.70, -13.30]
Ford 1994	255	86	10	262	86	10	12.3%	-7.00 [-82.38, 68.38]
Susanto 2008	275.6	87.6	16	282.9	65.6	16	24.3%	-7.30 [-60.92, 46.32]
Teichtahl 1996	377	95	20	391	99	20	19.4%	-14.00 [-74.13, 46.13]
Subtotal (95% CI)			**81**			**83**	**100.0%**	**-23.06 [-49.51, 3.40]**

Heterogeneity: Chi² = 3.85, df = 4 (P = 0.43); I² = 0%
Test for overall effect: Z = 1.71 (P = 0.09)

1.4.2 Duration >12weeks								
Kiljander-1 2006	334.9	102	105	338.7	123.5	111	15.1%	-3.80 [-33.94, 26.34]
Kiljander 2010	309	139.8	327	316	136.9	627	39.7%	-7.00 [-25.56, 11.56]
Kiljander-2 2006	320.1	113.3	171	325.2	121.5	174	22.3%	-5.10 [-29.88, 19.68]
Littner 2005	365	95	108	371	84	99	23.0%	-6.00 [-30.39, 18.39]
Subtotal (95% CI)			**711**			**1011**	**100.0%**	**-5.87 [-17.56, 5.83]**

Heterogeneity: Chi² = 0.04, df = 3 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.98 (P = 0.33)



Test for subgroup differences: Chi² = 1.36, df = 1 (P = 0.24), I² = 26.3%

D

Study or Subgroup	Placebo Mean	Placebo SD	Placebo Total	Proton Pump Inhibitor Mean	Proton Pump Inhibitor SD	Proton Pump Inhibitor Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 Omeprazole group								
Boeree 1998	335	98	13	322	109	15	27.3%	13.00 [-63.69, 89.69]
Ford 1994	255	86	10	262	86	10	28.3%	-7.00 [-82.38, 68.38]
Teichtahl 1996	377	95	20	391	99	20	44.4%	-14.00 [-74.13, 46.13]
Subtotal (95% CI)			**43**			**45**	**100.0%**	**-4.65 [-44.72, 35.43]**

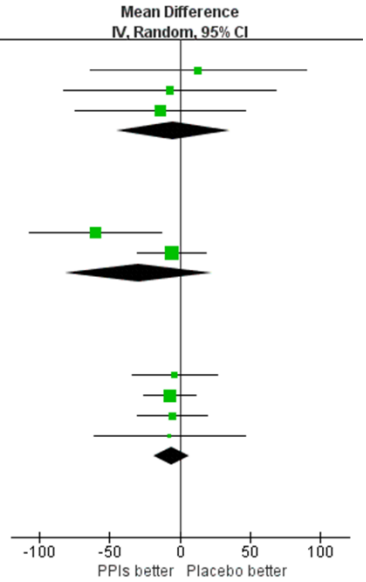
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 2 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)

1.3.2 Lansoprazole group								
dos Santos 2007	267	81	22	327	77	22	42.9%	-60.00 [-106.70, -13.30]
Littner 2005	365	95	108	371	84	99	57.1%	-6.00 [-30.39, 18.39]
Subtotal (95% CI)			**130**			**121**	**100.0%**	**-29.18 [-81.56, 23.21]**

Heterogeneity: Tau² = 1096.72; Chi² = 4.04, df = 1 (P = 0.04); I² = 75%
Test for overall effect: Z = 1.09 (P = 0.27)

1.3.3 Esomeprazole group								
Kiljander-1 2006	334.9	102	105	338.7	123.5	111	18.4%	-3.80 [-33.94, 26.34]
Kiljander 2010	309	139.8	327	316	136.9	627	48.6%	-7.00 [-25.56, 11.56]
Kiljander-2 2006	320.1	113.3	171	325.2	121.5	174	27.2%	-5.10 [-29.88, 19.68]
Susanto 2008	275.6	87.6	16	282.9	65.6	16	5.8%	-7.30 [-60.92, 46.32]
Subtotal (95% CI)			**619**			**928**	**100.0%**	**-5.91 [-18.84, 7.02]**

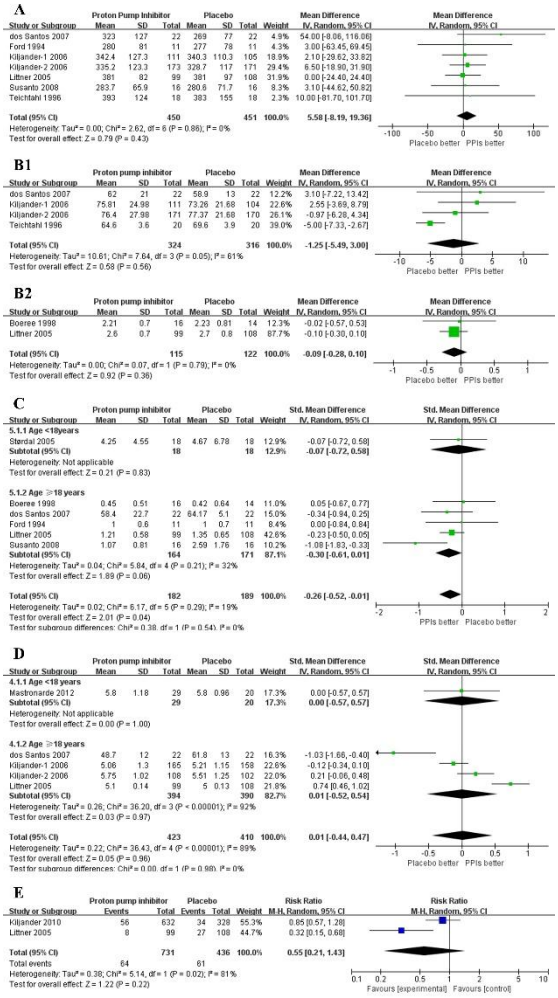
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 3 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.90 (P = 0.37)



Test for subgroup differences: Chi² = 0.73, df = 2 (P = 0.69), I² = 0%

<Original version>

Figure 5:



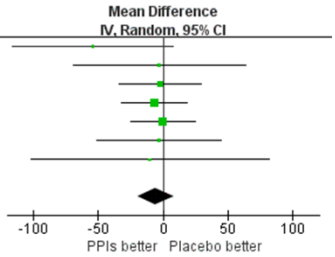
<Revised version>

Figure 5:

A

Study or Subgroup	Placebo Mean	Placebo SD	Placebo Total	Proton Pump Inhibitor Mean	Proton Pump Inhibitor SD	Proton Pump Inhibitor Total	Weight	Mean Difference IV, Random, 95% CI
dos Santos 2007	269	77	22	323	127	22	4.9%	-54.00 [-116.06, 8.06]
Ford 1994	277	78	11	280	81	11	4.3%	-3.00 [-69.45, 63.45]
Kiljander-1 2006	340.3	110.3	105	342.4	127.3	111	18.9%	-2.10 [-33.82, 29.62]
Kiljander-2 2006	328.7	117	171	335.2	123.3	173	29.4%	-6.50 [-31.90, 18.90]
Littner 2005	381	97	108	381	82	99	31.9%	0.00 [-24.40, 24.40]
Susanto 2008	280.6	71.7	16	283.7	65.9	16	8.3%	-3.10 [-50.82, 44.62]
Teichtahl 1996	383	155	18	393	124	18	2.3%	-10.00 [-101.70, 81.70]
Total (95% CI)			**451**			**450**	**100.0%**	**-5.58 [-19.36, 8.19]**

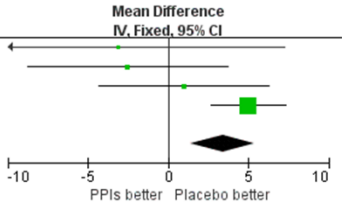
Heterogeneity: Tau² = 0.00; Chi² = 2.62, df = 6 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.79 (P = 0.43)



B1

Study or Subgroup	Placebo Mean	Placebo SD	Placebo Total	Proton pump inhibitor Mean	Proton pump inhibitor SD	Proton pump inhibitor Total	Weight	Mean Difference IV, Fixed, 95% CI
dos Santos 2007	58.9	13	22	62	21	22	3.7%	-3.10 [-13.42, 7.22]
Kiljander-1 2006	73.26	21.68	104	75.81	24.98	111	10.1%	-2.55 [-8.79, 3.69]
Kiljander-2 2006	77.37	21.68	170	76.4	27.98	171	13.9%	0.97 [-4.34, 6.28]
Teichtahl 1996	69.6	3.9	20	64.6	3.6	20	72.4%	5.00 [2.67, 7.33]
Total (95% CI)			**316**			**324**	**100.0%**	**3.38 [1.40, 5.36]**

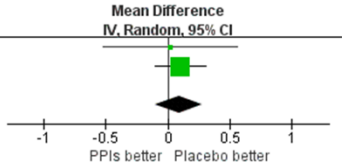
Heterogeneity: Chi² = 7.64, df = 3 (P = 0.05); I² = 61%
Test for overall effect: Z = 3.35 (P = 0.0008)



B2

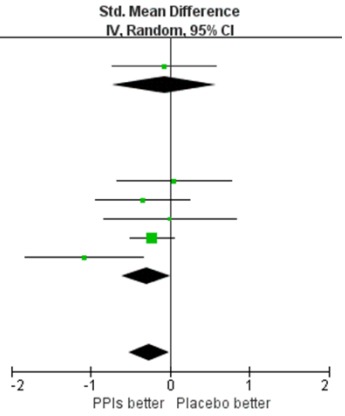
Study or Subgroup	Placebo Mean	Placebo SD	Placebo Total	Proton pump inhibitor Mean	Proton pump inhibitor SD	Proton pump inhibitor Total	Weight	Mean Difference IV, Random, 95% CI
Boeree 1998	2.23	0.81	14	2.21	0.7	16	12.3%	0.02 [-0.53, 0.57]
Littner 2005	2.7	0.8	108	2.6	0.7	99	87.7%	0.10 [-0.10, 0.30]
Total (95% CI)			**122**			**115**	**100.0%**	**0.09 [-0.10, 0.28]**

Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.92 (P = 0.36)



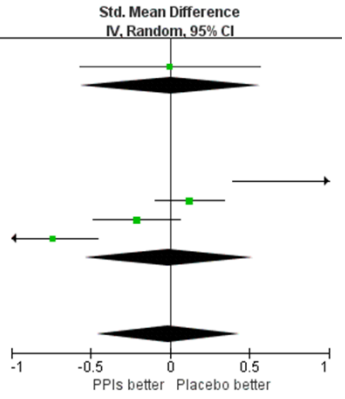
C

Study or Subgroup	Proton pump inhibitor Mean	Proton pump inhibitor SD	Proton pump inhibitor Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.1.1 Age <18years								
Størdal 2005	4.25	4.55	18	4.67	6.78	18	12.9%	-0.07 [-0.72, 0.58]
Subtotal (95% CI)			**18**			**18**	**12.9%**	**-0.07 [-0.72, 0.58]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.21 (P = 0.83)								
5.1.2 Age ⩾18 years								
Boeree 1998	0.45	0.51	16	0.42	0.64	14	11.0%	0.05 [-0.67, 0.77]
dos Santos 2007	58.4	22.7	22	64.17	5.1	22	15.0%	-0.34 [-0.94, 0.25]
Ford 1994	1	0.6	11	1	0.7	11	8.4%	0.00 [-0.84, 0.84]
Littner 2005	1.21	0.58	99	1.35	0.65	108	42.6%	-0.23 [-0.50, 0.05]
Susanto 2008	1.07	0.81	16	2.59	1.76	16	10.2%	-1.08 [-1.83, -0.33]
Subtotal (95% CI)			**164**			**171**	**87.1%**	**-0.30 [-0.61, 0.01]**
Heterogeneity: Tau² = 0.04; Chi² = 5.84, df = 4 (P = 0.21); I² = 32%								
Test for overall effect: Z = 1.89 (P = 0.06)								
Total (95% CI)			**182**			**189**	**100.0%**	**-0.26 [-0.52, -0.01]**
Heterogeneity: Tau² = 0.02; Chi² = 6.17, df = 5 (P = 0.29); I² = 19%								
Test for overall effect: Z = 2.01 (P = 0.04)								
Test for subgroup differences: Chi² = 0.38, df = 1 (P = 0.54), I² = 0%								



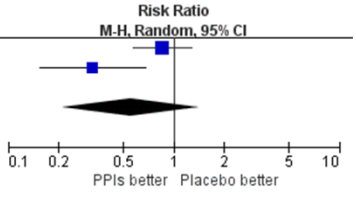
D

Study or Subgroup	Placebo Mean	Placebo SD	Placebo Total	Proton pump inhibitor Mean	Proton pump inhibitor SD	Proton pump inhibitor Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.1.1 Age <18 years								
Mastronarde 2012	5.8	0.96	20	5.8	1.18	29	17.3%	0.00 [-0.57, 0.57]
Subtotal (95% CI)			**20**			**29**	**17.3%**	**0.00 [-0.57, 0.57]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
4.1.2 Age ⩾18 years								
dos Santos 2007	61.8	13	22	48.7	12	22	16.3%	1.03 [0.40, 1.66]
Kiljander-1 2006	5.21	1.15	158	5.06	1.3	165	22.6%	0.12 [-0.10, 0.34]
Kiljander-2 2006	5.51	1.25	102	5.75	1.02	108	22.0%	-0.21 [-0.48, 0.06]
Littner 2005	5	0.13	108	5.1	0.14	99	21.8%	-0.74 [-1.02, -0.46]
Subtotal (95% CI)			**390**			**394**	**82.7%**	**-0.01 [-0.54, 0.52]**
Heterogeneity: Tau² = 0.26; Chi² = 36.20, df = 3 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 0.03 (P = 0.97)								
Total (95% CI)			**410**			**423**	**100.0%**	**-0.01 [-0.47, 0.44]**
Heterogeneity: Tau² = 0.22; Chi² = 36.43, df = 4 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 0.05 (P = 0.96)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.98), I² = 0%								



E

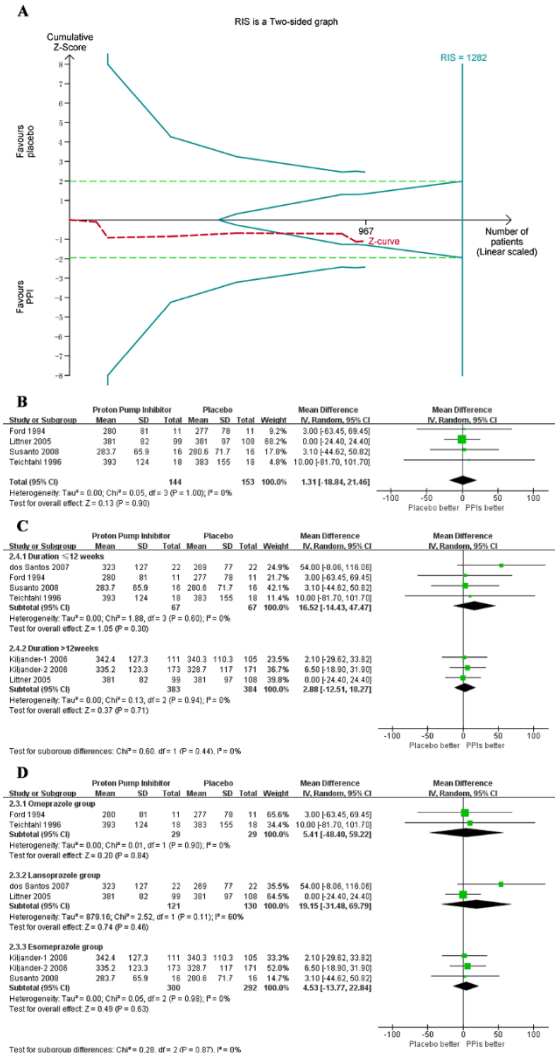
Study or Subgroup	Proton pump inhibitor Events	Proton pump inhibitor Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Kiljander 2010	56	632	34	328	55.3%	0.85 [0.57, 1.28]
Littner 2005	8	99	27	108	44.7%	0.32 [0.15, 0.68]
Total (95% CI)		**731**		**436**	**100.0%**	**0.55 [0.21, 1.43]**
Total events	64		61			
Heterogeneity: Tau² = 0.38; Chi² = 5.14, df = 1 (P = 0.02); I² = 81%						
Test for overall effect: Z = 1.22 (P = 0.22)						



Appendix:

<Original version>

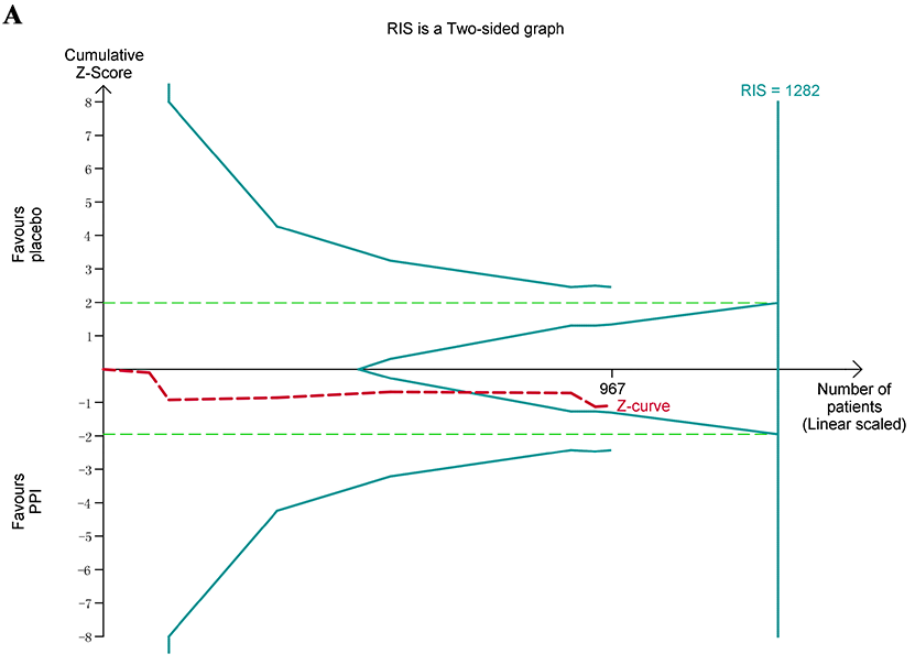
Figure S2b:



<Revised version>

Figure S3b:

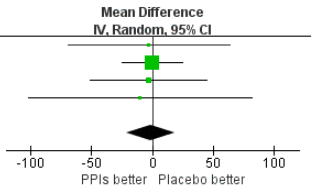
A



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)



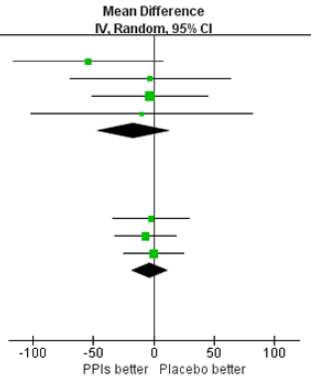
C

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)



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]**

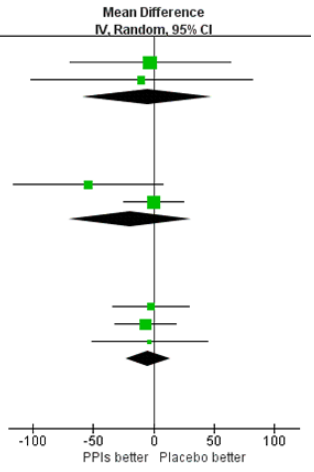
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)

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)



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

Comment 2: Page 9, line 54: the Authors report “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] ….”. However, I see only one study (Dos Santos 2007) showing improvement from Figure 3A. Please amend the text accordingly.

Reply:

We truly appreciate your careful review of our paper and this comment. We have modified the text in the correspondent part of the **Results** (Page 9: line 56):

<Original version>

Three of eleven studies found a significant improvement on mPEF.[14 18 20]

<Revised version>

Only one of the studies with data available found a significant improvement on mPEF.[19]

Comment 3: Page 6, line 45. Authors report: “This review was restricted to studies with treatment duration of 4 weeks and above”. Please indicate in the Results whether there were studies with duration less than 4 weeks. If studies were presented please discuss whether this might affect the results of the review.

Reply:

Thank you very much for this comment by the review. With the thorough literature search, there is no other studies with duration less than 4 weeks. Besides, the treatment duration of at least 4 weeks was recommended for the therapy of gastroesophageal reflux disease with the application of PPIs. We have added the appropriate portion in the **Results** (Page 9: line 8) regarding this comment.

<Revised version>

All studies conducted lasted for more than 4 weeks.

Comment 4: Page 10. Subgroup analysis should be written in a better way. I suggest to split the period in separate paragraphs. Please add consistently number of studies and number of population for each of the subgroup analysis.

Reply:

We greatly appreciate the suggestions by the reviewer. We have modified the format of the paragraphs of the subgroup analysis and added the corresponding parts of the **Results** (Page 10 line 23-page 11 line 6):

<Original version>

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**).

<Revised version>

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**).

Comment 5: Pages 11-12. Please add number of participants as necessary. Figure citation should be placed after heterogeneity description.

Reply:

We sincerely thank the reviewer for this comment. We have added the number of populations and modified the figure citation errors in the **Results**:

<Revised version>

Line	Original version	Revised version
P10:	The overall analysis found no statistically significant benefit on mPEF with PPIs	The overall analysis found no statistically significant benefit on mPEF

L9	treatment (8.68 L/min, 95% CI [-2.35, 19.37], P=0.11) (Figure 3 A). Heterogeneity was absent (I2=0%; P=0.73).	with PPIs treatment (8.68 L/min, 95% CI [-2.35, 19.37], P=0.11). Heterogeneity was absent (I2=0%; P=0.73) (Figure 3 A).
P11: L21	Of these 10 trials, 6 studies provided information and were included in the meta-analyses.	Of these 10 trials, 6 studies provided information and were included in the meta-analyses (901 participants).
P11: L49	Three studies provided information of FEV1 % predicted,[12 18 19] and only two provided available data of FEV1 (L),[13 16] which were included in analyses, respectively.	Three studies with a population of 640 provided information of FEV1 % predicted,[12 18 19] and only two with 237 participants provided available data of FEV1 (L),[13 16] which were included in analyses, respectively.
P12: L11	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.	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).
P12: L33	Four eligible studies were included for meta-analysis.	Four eligible studies were included for meta-analysis (853 subjects).
P12: L49	Only two studies provided information of episodes of asthma exacerbation and showed an improvement in this variance.	Only two studies including 1167 patients provided information of episodes of asthma exacerbation and showed an improvement in this variance.

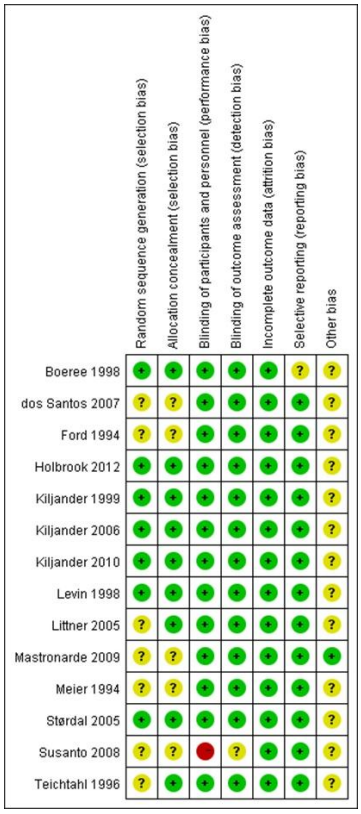
Comment 6: The risk of selectively reporting bias looks like unclear only in one study. However, since authors underlined the fact that some data and/or relevant outcomes were not reported or available this particular item of the risk of bias should be revised.

Reply:

We sincerely thank the reviewer for this comment. We agree with the reviewer and revised this error in **Figure 2** (Page 25).

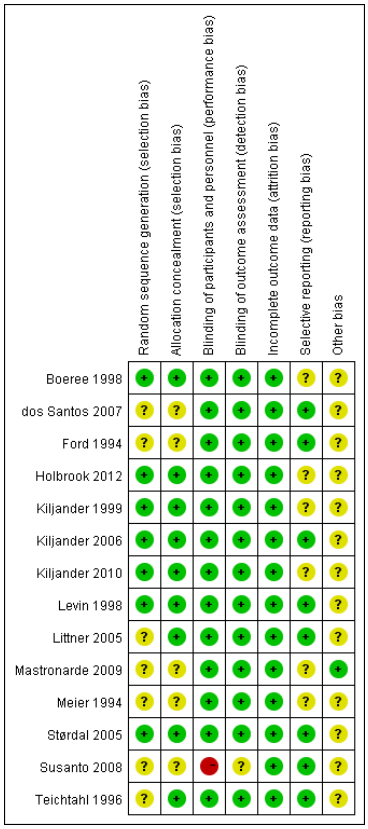
<Original version>

Figure 2:



<Revised version>

Figure 2:



Other than the revision mentioned above, some minor changes were also made to ensure the consistency and fluency of the article or to correct the mistakes that was not noticed previously.

VERSION 2 – REVIEW

REVIEWER	Tianwen Lai Department of Respiratory and Critical Care Medicine, The Affiliated Hospital of Guangdong Medical University
REVIEW RETURNED	04-Jun-2021

GENERAL COMMENTS	The authors have addressed the points raised in my previous review.

REVIEWER	Iosief Abraha Servizio Immunostrasfusionale, USL Umbria 2, Foligno, Italy
REVIEW RETURNED	06-Jun-2021

GENERAL COMMENTS	The revised version was satisfactory