Supplementary Table 1. Conflict of Interest Register

Name	Relevant employee experience	Relevant consultation experience	Personal ownership interest	Non-personal pecuniary interest	Relevant honorarium experience	Action required
Hye-Kyung Jung	None	None	None	None	None	None
Chung Hyun Tae	None	None	None	None	None	None
Kyung Ho Song	None	None	None	None	None	None
Seung Joo Kang	None	None	None	None	None	None
Jong Kyu Park	None	None	None	None	None	None
Jeong Eun Shin	None	None	None	None	None	None
Hyun Chul Lim	None	None	None	None	None	None
Sang Kil Lee	None	None	None	None	None	None
Da Hyun Jung	None	None	None	None	None	None
Yoon Jin Choi	None	None	None	None	None	None
Seung In Seo	None	None	None	None	None	None
Joon Sung Kim	None	None	None	None	None	None
Jung Min Lee	None	None	None	None	None	None
Beom Jin Kim	None	None	None	None	None	None
Sun Hyung Kang	None	None	None	None	None	None
Chan Hyuk Park	None	None	None	Received research funding from Daewoong Pharmaceutical, Hanmi Pharmaceutical, and CJ HealthCare	None	None
Suck Chei Choi	None	None	None	None	None	None
Joong Goo Kwon	None	None	None	Received research funding for ilaprazole in NERD from IL-YANG PHARM, and tegoprazan in GERD from HK inno. N Corp	None	None
Kyung Sik Park	None	None	None	None	None	None
Moo In Park	None	None	None	None	None	None
Tae Hee Lee	None	None	None	None	None	None
Seung Young Kim	None	None	None	None	None	None
Young Sin Cho	None	None	None	None	None	None
Han Hong Lee	None	None	None	None	None	None
Eun Jeong Gong	None	None	None	None	None	None
Kee Wook Jung	None	None	None	Received research funding for tegoprazan from HK inno. N Corp	None	None
Do Hoon Kim	None	None	None	None	None	None
Hee Seok Moon	None	None	None	None	None	None
Hirota Miwa	None	None	None	Received research funding Pharmaceutical Co, Ltd, Otsuka Pharmaceutical Co, Ltd, Astra Zeneca Co, Ltd	Received honorarium from Takeda Pharmaceutical Co, Ltd, Otsuka Pharmaceutical Co, Ltd, Astra Zeneca Co, Ltd, Eisai Co, Ltd	None
Chien-Lin Chen	None	None	None	None	None	None
Sutep Gonlachanvit	None	None	None	None	Received lecturer's fees from Takeda Pharmaceutical Co, Ltd, and Otsuka Pharmaceutical Co, Ltd	None
Uday C Ghoshal	None	None	None	None	None	None
Justin C Wu	None	None	None	None	None	
Kewin T H Siah	None	None	None	None	None	None
Xiaohua Hou	None	None	None	None	None	None
Tadayuki Oshima	None	None	None	None	None	None
Mi-Young Choi	None	None	None	None	None	None
Kwang Jae Lee	None	None	None	None	None	None

NERD, non-erosive reflux disease; GERD, gastroesophageal reflux disease.

Supplementary Table 2. Key Questions and Keywords Used in Meta-analyses

Key questions	Keywords
Is GERD increasing in Asia?	Gastroesophageal reflux, esophagitis, gastroesophageal, gastric acid, esophageal, GERD, GER, ERD, prevalence, epidemiology
Is a 2-week trial of a standard dose of PPI useful as a sensitive and practical test for GERD diagnosis in patients with typical GERD symptoms compared to 24-hour ambulatory pH-impedance monitoring?	Gastroesophageal reflux disease, erosive esophagitis, non-erosive esophagitis, a proton-pump inhibitor, omeprazole, esomeprazole, rabeprazole, pantoprazole, lansoprazole, ilaprazole, dexlansoprazole, wireless pH monitoring, impedance-pH monitoring, ambulatory reflux monitoring, pH monitoring, sensitivity, specificity
Is a double dose proton pump inhibitor effective for alleviating symptoms in patients with GERD who have insufficient effectiveness with standard proton pump inhibitors?	Proton pump inhibitor, PPI(s), acid suppression, acid suppression therapy, omeprazole, esomeprazole, rabeprazole, pantoprazole, lansoprazole, ilaprazole, dexlansoprazole, standard dose, high dose, double dose
Has on-demand PPI therapy more effective than continuous daily PPI therapy for the long-term management of patients with NERD or mild ERD?	Gastroesophageal reflux, esophagitis, heartburn, gastric acid reflux, esophageal reflux, GERD, GER, proton pump inhibitor, maintenance, recurrence, omeprazole, esomeprazole, rabeprazole, pantoprazole, lansoprazole, ilaprazole, dexlansoprazole, on-demand, on-demand, continuous, intermittent
Are proton pump inhibitors recommended to treat non-cardiac chest pain in patients with typical GERD symptoms?	Noncardiac chest pain, non-cardiac chest pain, atypical chest pain, functional chest pain, NCCP, proton pump inhibitor, proton pump inhibitors, omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, dexlansoprazole, ilaprazole, randomized controlled trial, controlled clinical trial, randomized, placebo, drug therapy, randomly, trial, groups
Are PPIs recommended for patients with Barrett's esophagus to reduce the risk of progression to high-grade dysplasia or adenocarcinoma?	Barrett, PPI, proton-pump inhibitor(s), proton pump inhibitor(s), omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, dexlansoprazole, ilaprazole, acid suppression, acid-suppressive, cancer(s), carcinoma(s), adenocarcinoma(s), dysplasia(s)
Are there potential risks associated with long-term proton pump inhibitor treatment?	Proton pump inhibitor, PPI(s), acid suppression, acid suppression therapy, omeprazole, esomeprazole, rabeprazole, pantoprazole, lansoprazole, ilaprazole, dexlansoprazole, clostridium difficile, clostridium infection, CDI, pseudomembranous colitis, *Clostridium difficile* (*C. difficile*) infection, *Clostridium difficile* (*C. difficile*)-associated diarrhea (CDAD), infection, diarrhea, colitis
Is the effect of P-CAB comparable with that of PPIs for the initial treatment of patients with GERD?	Potassium-competitive, P-CAB, vonoprazan, TAK-438, Takecab, tegoprazan, CJ12420, gastroesophageal reflux disease, GERD, nonerosive reflux disease, NERD, erosive re esophagitis, reflux
Does the combination of dose prokinetics with PPI improve GERD symptoms more than PPI monotherapy?	Gastroesophageal reflux disease, gastroesophageal reflux disease, gastroesophageal reflux, non-erosive reflux disease, reflux esophagitis, erosive reflux disease, endoscopy-negative reflux disease, proton pump inhibitor, prokinetic, prokinetics, erythromycin, metoclopramide, domperidone, cisapride, mosapride, itopride, ABT-229, alosetron, tegaserod, acotiamide, prucalopride, DA-9701, rikkunshito, promotility, relamorelin, cinitapride, ghrelin, revexepride, TZP-101, TZP-102

GERD, gastroesophageal reflux disease; GER, gastroesophageal reflux; ERD, erosive reflux disease; PPI, proton pump inhibitor; NERD, non-erosive reflux disease; NCCP, non-cardiac chest pain; CDI, *Clostridium difficile* infection; CDAD, *Clostridium difficile*-associated diarrhea; P-CAB, potassium competitive acid blocker.

Supplementary Table 3. Asian Studies Included on the Meta-analyses of Acid Exposure Time in 24-Hour Ambulatory pH Monitoring

First author	Year	Country	n	Mean AET (%)	ULN of AET (%)	Estimation method[a]
Yano et al[89]	2017	Japan	20	0.9	2.7	A
Netinatsunton et al[90]	2016	Thailand	34	0.5	1.9	A
Wu et al[91]	2007	Hong Kong	28	0.2	0.6	A
Wu et al[92]	1999	China	20	1.3	3.5	A
Moon et al[93]	2008	Korea	30	1.6[b]	5.1	Bc
Ferdinandis et al[94]	2006	Sri Lanka	12	1.5[b]	3.5	Bd
Ho and Kang[95]	2000	Singapore	15	1.9[b]	4.0	Bd
Saraswat et al[96]	1994	India	16	1.7[b]	3.0	Bd
Kim et al[97]	2008	Korea	50	1.3	4.0	C
Chun et al[98]	2000	Korea	25	1.4	3.6	Cc
Xiao et al[99]	2012	China	20	0.6[b]	2.4	D
Ishimura et al[100]	2015	Japan	10	1.1	4.2	D
Kawamura et al[101]	2016	Japan	42	NA	3.3	E
Wang et al[102]	2011	China	37	NA	3.1	E
Xiao et al[103]	2009	China	70	NA	2.7	E
Hu et al[104]	2002	Hong Kong	20	NA	4.6	E
Amarasiri et al[105]	2012	Sri Lanka	30	NA	1.5	E
Yi et al[106]	2005	Taiwan	21	NA	7.0	E
Kawamura et al[107]	2011	Japan	10	0.3	1.2	Fd

[a]Estimation method: (A) if mean with standard deviation (SD) is present, upper limit of normal (ULN) is estimated by mean + 2SD, (B) if median (range) is present, mean and SD is calculated, and ULN is estimated with mean + 2SD, (C) if both mean with SD and median (range) are present, mean and SD is estimated by median (range) value, and ULN is estimated by mean + 2SD, (D) if median with interquartile range (IQR) is present, mean and SD is calculated, and ULN is estimated with mean + 2SD, (E) 95th percentile is present despite insufficiency of other data, ULN is determined as the presented 95th percentile, (F) if mean (range) is present, mean is used to calculate ULN, cif 95th percentile is present and is greater than estimated ULN using mean + 2SD, 95th percentile is used, and dif the maximum is present and is lower than estimated ULN using mean ± 2SD, maximum is used.
[b]Calculated value.
AET, acid exposure time; ULN, upper limit of normal; NA, not applicable.

Supplementary Table 4. Summary of the Evidence Supporting Weight Reduction in Patients With Gastroesophageal Reflux Disease

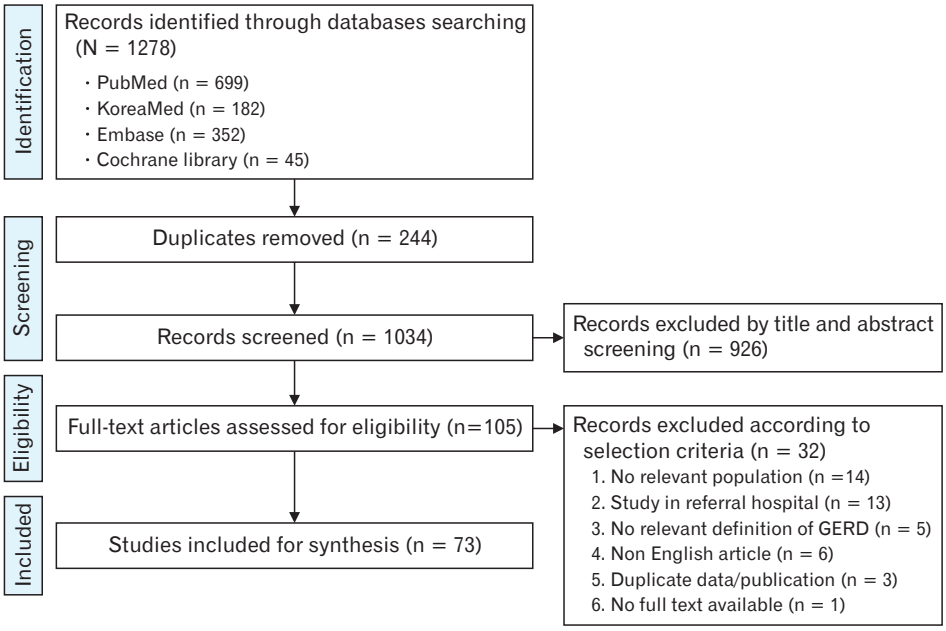
Reference	Study design	Number of patients	Mean BMI at baseline (kg/m^2)	Intervention	Follow-up duration	Outcome
De Bortoli et al,[141] 2016	Prospective open-label study	217	30.5 ± 4.0	Calorie-restricted diet (60% carbohydrate, 25% fat, and 15% protein) with aerobic exercise (weight loss of 10%) vs control	6 mo	Decreased symptom score Reduction or discontinuation of proton pump inhibitor
Singh et al,[134] 2013	Prospective cohort study, single-arm	332	34.7 ± 4.6	Face-to-face or phone-based weight management program	6 mo	Improvement in reflux symptoms
Ness-Jensen et al,[142] 2013	Prospective population-based cohort study	29 610	26	No intervention		Dose-dependent symptom reduction and treatment success
Mathus-Vliegen and Tygat,[143] 2002	Randomized controlled trials	34	43.4 ± 6.6	Intragastric balloon vs sham	65 wk	Improved reflux parameters
Fraser-Moodie,[144] 1999	Prospective study, single-arm	34	23.5 ± 2.3	Dietary advice	26 wk	Decreased symptom score
Kjellin et al,[145] 1996	Randomized controlled trials	20	31.4 (range 28-42)	Very low caloric diet for 6 weeks vs. control	6 mo	No improvement in reflux symptoms or objective measurements

Data are presented as mean ± SD.

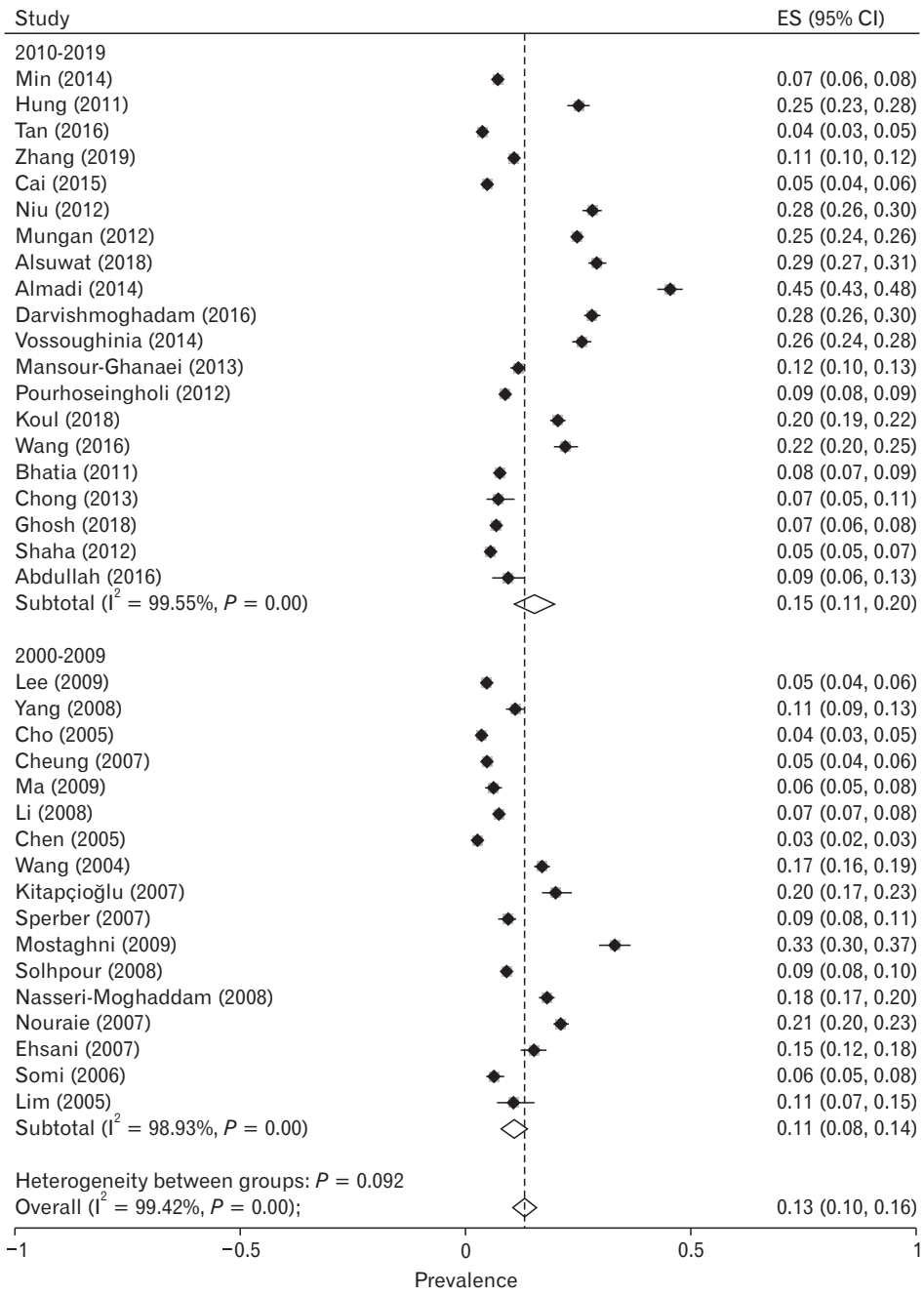
Supplementary Table 5. Summary of Direct Comparison Trials Between the Efficacy of On-demand Proton Pump Inhibitor and Continuous Daily Proton Pump Inhibitor in the Long-term Management of Patients With Gastroesophageal Reflux Disease

Reference	Study design	Population	On-demand vs Continuous	Follow-up duration	Outcomes of the failure of PPI treatment
Jassen et al,[171]	RCT	NERD and mild esophagitis treated with P 20 mg QD for 4 wk	P 20 mg vs P 20 mg	6 mo	Premature discontinuation due to insufficient symptom control
Hansen et al,[170] 2005	RCT	Uninvestigated GERD received E 40 mg QD for 4 wk	E 20 mg vs E 20 mg	6 mo	Relapse is defined if they need a change in therapy, such as experiencing a relapse in symptoms
Sjöstedt et al,[169] 2005	RCT	Investigated GERD (LA grades A-D), with endoscopically healed after E 40 mg QD for 4-8 wk	E 20 mg vs E 20 mg	6 mo	Relapse defined as if moderate or severe heartburn persisted for 3 consecutive days
Morgan et al,[168] 2007	RCT	Minimum 3-month history of GERD who did on continuous daily PPI therapy for at least one month	R 20 mg vs R 20 mg	6 mo	Discontinuing for inadequate heartburn control
Szucs et al,[167] 2009	RCT	Uninvestigated patients with GERD who demonstrated complete relief of symptoms after an initial treatment of 4 wk with E 40 mg	E 20 mg vs E 20 mg	26 wk	Relapse is defined as the "need for a change of therapy."
van der Velden et al,[166] 2010	RCT	Continuous proton pump inhibitor or histamine-2-receptor antagonist) for > 6 mo	P 20 mg vs P 20 mg	13 wk	Discontinuing for inadequate relief and usage of rescue medication
Bayerdörffer et al,[165] 2016	RCT	NERD who were heartburn-free after 4 wk' treatment with E 20 mg daily	E 20 mg vs E 20 mg	6 mo	Premature discontinuation due to unsatisfactory treatment

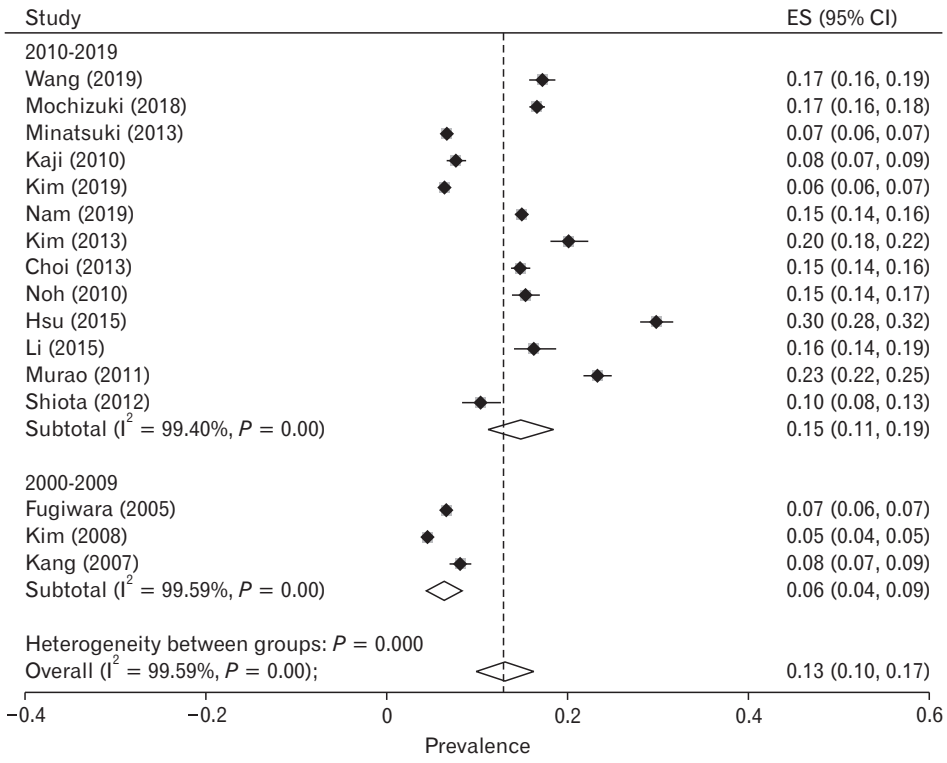
PPI, proton pump inhibitor; RCT, randomized controlled trial; NERD, non-erosive reflux disease; P, pantoprazole; E, esomeprazole; R, rabeprazole; QD, once a day; GERD, gastroesophageal reflux disease; LA, Los Angeles classification.



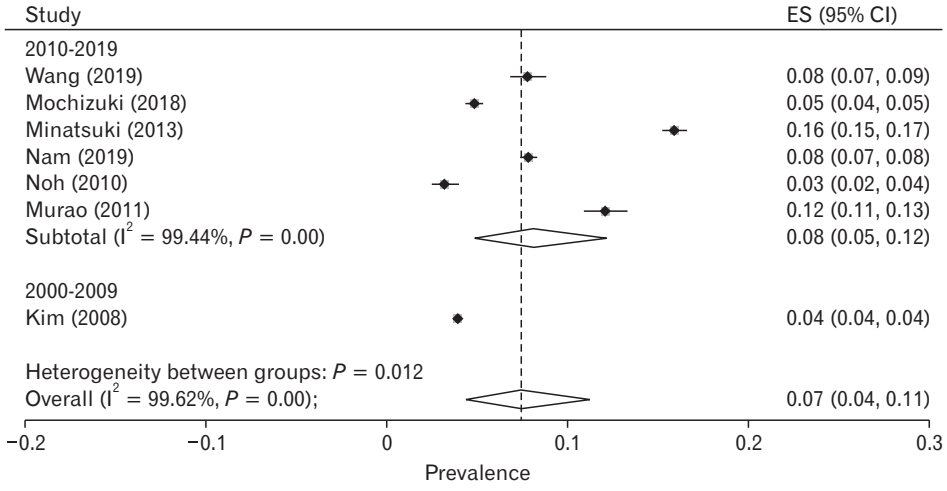
Supplementary Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram of the systematic review process of the epidemiology of gastroesophageal reflux disease in Asia.



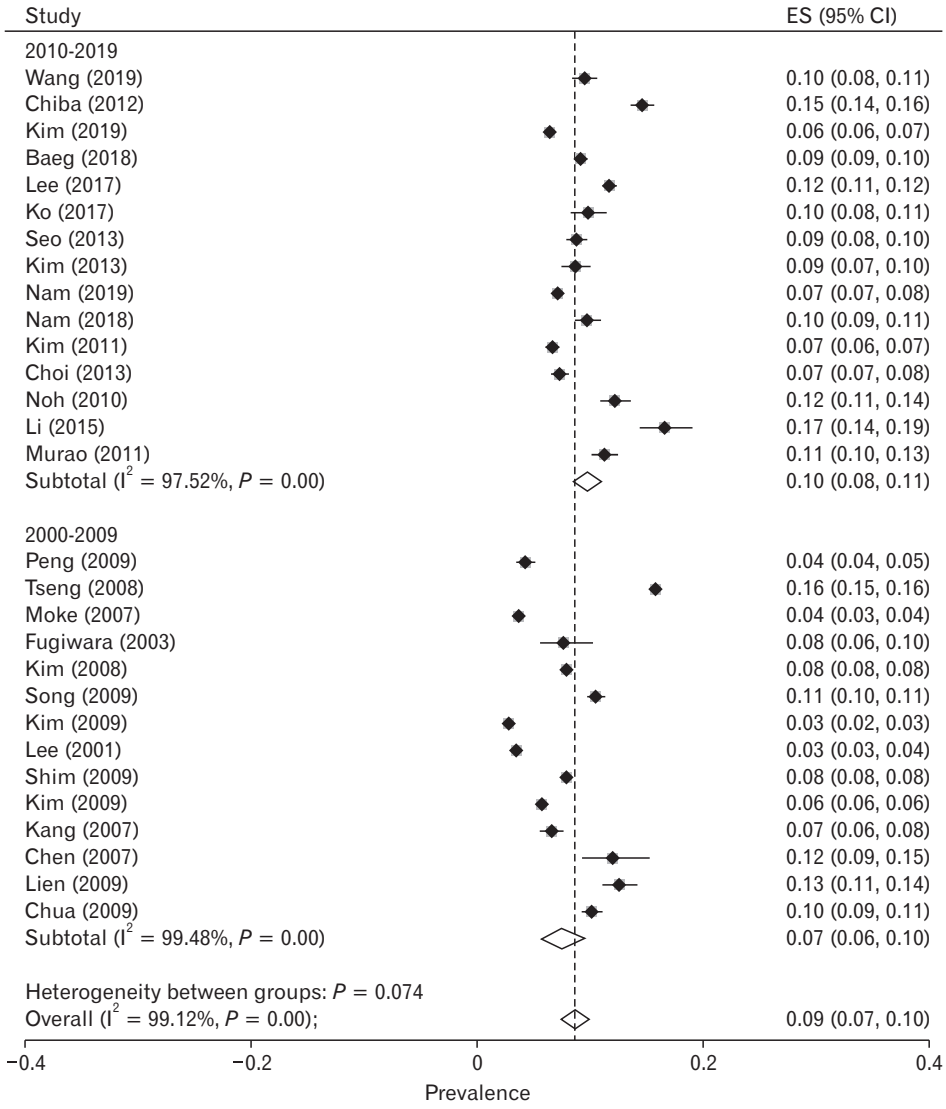
Supplementary Figure 2. Forest plot comparison of the prevalence of gastroesophageal reflux disease in population-based studies for 2 periods, 2000-2009 and 2010-2019. ES, effect size.



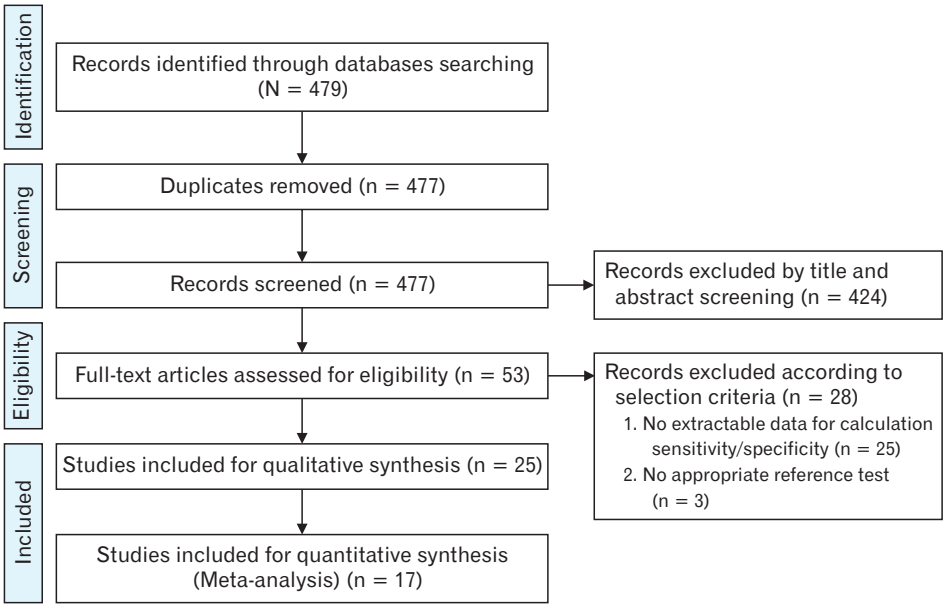
Supplementary Figure 3. Forest plot comparison of the prevalence of gastroesophageal reflux disease in observational studies of subjects who underwent medical check-ups in 2000-2009 and 2010-2019. ES, effect size.



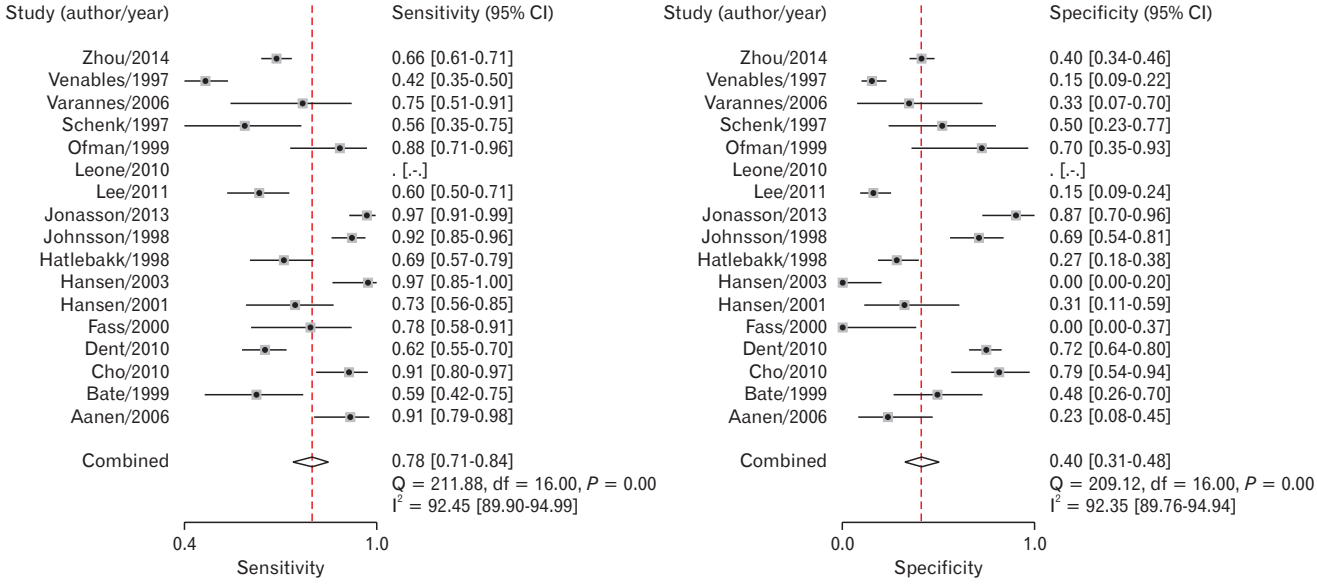
Supplementary Figure 4. Forest plot comparison of non-erosive reflux disease prevalence in observational studies of subjects who underwent medical check-ups in 2000-2009 and 2010-2019. ES, effect size.



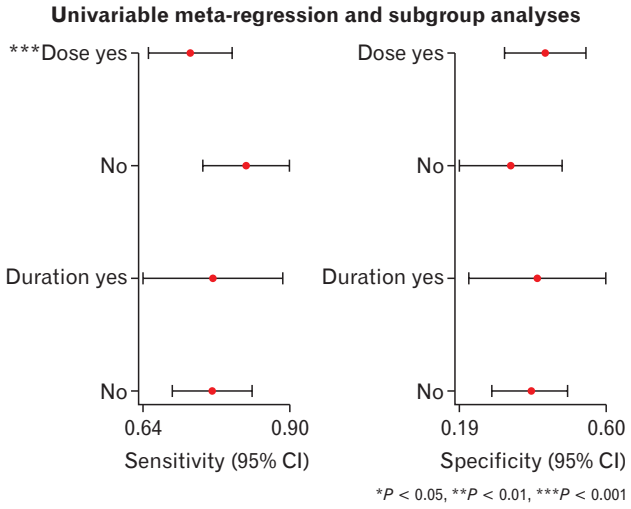
Supplementary Figure 5. Forest plot comparison of the prevalence of erosive reflux disease in observational studies of subjects who underwent medical check-ups in 2000-2009 and 2010-2019. ES, effect size.



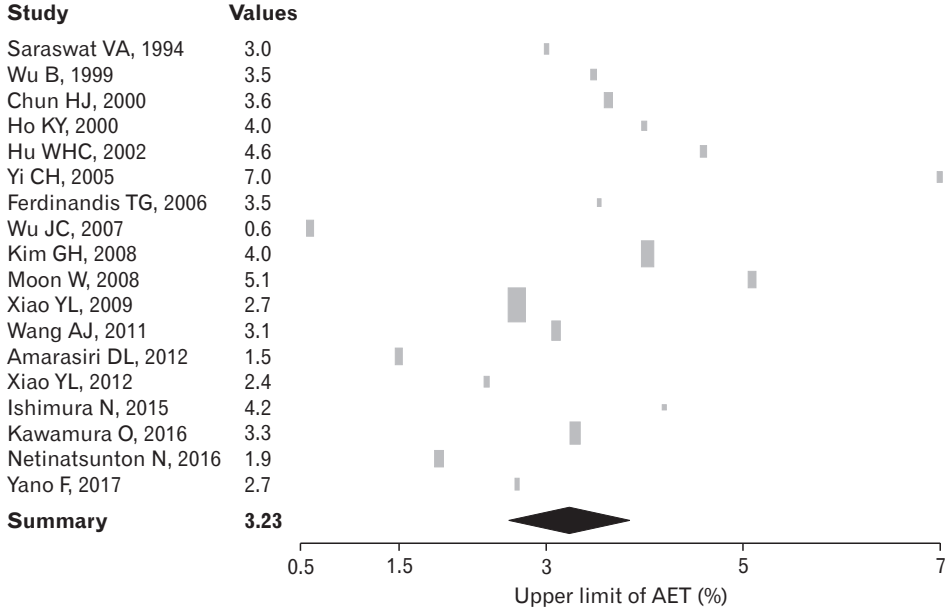
Supplementary Figure 6. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram of the systematic review process of the diagnostic performance of empirical proton pump inhibitors in gastroesophageal reflux disease.



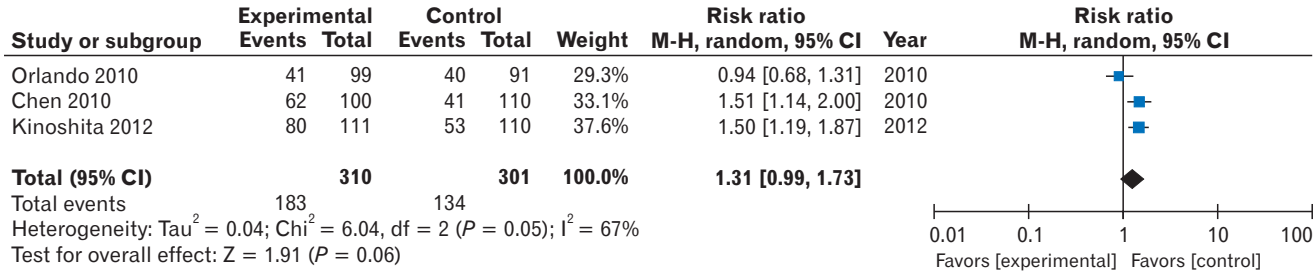
Supplementary Figure 7. Forest plot of sensitivity and specificity in a trial of proton pump inhibitors.



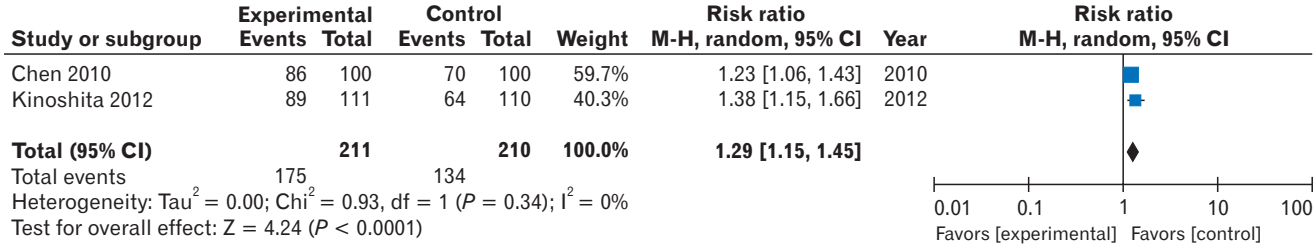
Supplementary Figure 8. Forest plot of subgroup analysis of dose (single versus double) and duration (< 2 weeks versus > 2 weeks) of proton pump inhibitors.



Supplementary Figure 9. Forest plot of upper limits of normal for the acid exposure time (AET [%]) in Asian studies.



Supplementary Figure 10. Forest plot of symptom resolution in the double and standard dose proton pump inhibitor at 4 weeks in patients with gastroesophageal reflux disease. M-H, Mantel-Haenszel.

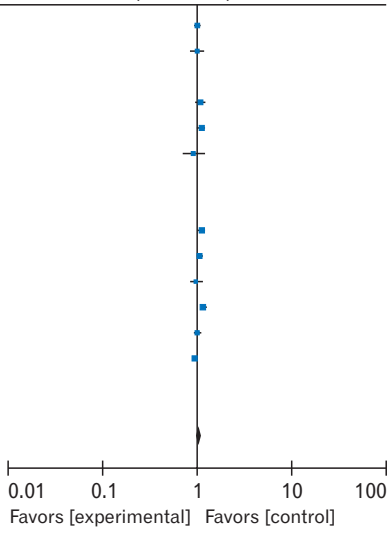


Supplementary Figure 11. Forest plot of symptom resolution in the double and standard dose proton pump inhibitor at 8 weeks. M-H, Mantel-Haenszel.

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk ratio M-H, random, 95% CI
Armstrong 2004	485	772	686	1114	10.6%	1.02 [0.95, 1.10]
Bardhan 2007	137	214	129	204	6.3%	1.01 [0.88, 1.17]
Castell 2002	0	0	0	0		Not estimable
Eggleston 2009	302	469	272	464	8.7%	1.10 [0.99, 1.22]
Fennerty 2005	344	478	307	483	9.5%	1.13 [1.04, 1.24]
Gilesen 2004	54	114	57	113	2.8%	0.94 [0.72, 1.23]
Glatzel 2007	0	0	0	0		Not estimable
Howden 2002	0	0	0	0		Not estimable
Kahrilas 2000	402	621	357	624	9.4%	1.13 [1.03, 1.24]
Labenz 2005	1187	1562	1112	1589	12.3%	1.09 [1.04, 1.13]
Moraes-Filho 2014	165	270	170	278	6.9%	1.00 [0.87, 1.14]
Richter 2001	831	1216	702	1209	11.2%	1.18 [1.11, 1.25]
Schmitt 2006	374	576	361	572	9.6%	1.03 [0.94, 1.12]
Scholten 2003	103	105	111	112	12.7%	0.99 [0.96, 1.02]
Zheng 2009	0	0	0	0		Not estimable
Total (95% CI)		**6397**		**6762**	**100.0%**	**1.06 [1.01, 1.12]**
Total events	4384		4264			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 48.29$, df = 10 ($P < 0.00001$); $I^2 = 79\%$

Test for overall effect: Z = 2.44 ($P = 0.01$)

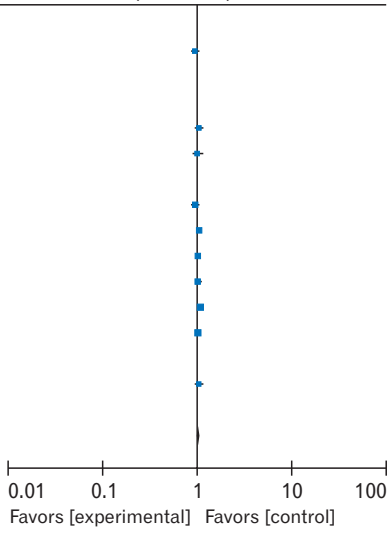


Supplementary Figure 12. Forest plot of symptom relief in subjects on esomeprazole 40 mg per day and other standard dose proton pump inhibitors at 4 weeks. M-H, Mantel-Haenszel.

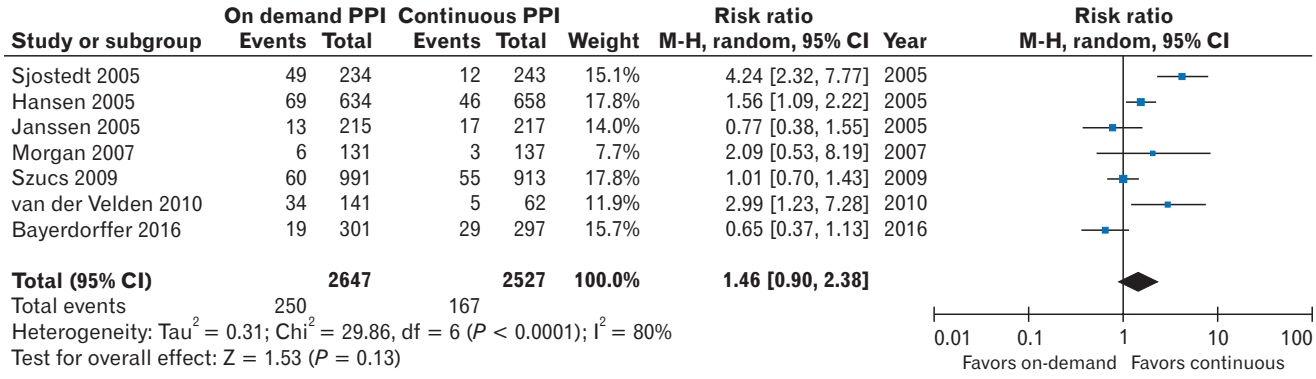
Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk ratio M-H, random, 95% CI
Armstrong 2004	0	0	0	0		Not estimable
Bardhan 2007	243	293	248	288	8.0%	0.96 [0.90, 1.03]
Castell 2002	0	0	0	0		Not estimable
Eggleston 2009	0	0	0	0		Not estimable
Fennerty 2005	410	498	388	501	8.9%	1.06 [1.00, 1.13]
Gilesen 2004	70	76	69	77	5.2%	1.03 [0.93, 1.14]
Glatzel 2007	0	0	0	0		Not estimable
Howden 2002	123	138	127	139	7.2%	0.98 [0.90, 1.05]
Kahrilas 2000	615	654	565	650	12.7%	1.08 [1.04, 1.12]
Labenz 2005	1431	1562	1413	1589	14.4%	1.03 [1.01, 1.05]
Moraes-Filho 2014	253	279	246	284	9.3%	1.05 [0.99, 1.11]
Richter 2001	1139	1216	1018	1209	13.7%	1.11 [1.08, 1.14]
Schmitt 2006	531	576	514	572	12.6%	1.03 [0.99, 1.06]
Scholten 2003	0	0	0	0		Not estimable
Zheng 2009	62	65	178	199	7.8%	1.07 [0.99, 1.15]
Total (95% CI)		**5357**		**5508**	**100.0%**	**1.04 [1.02, 1.07]**
Total events	4877		4766			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 32.49$, df = 9 ($P = 0.0002$); $I^2 = 72\%$

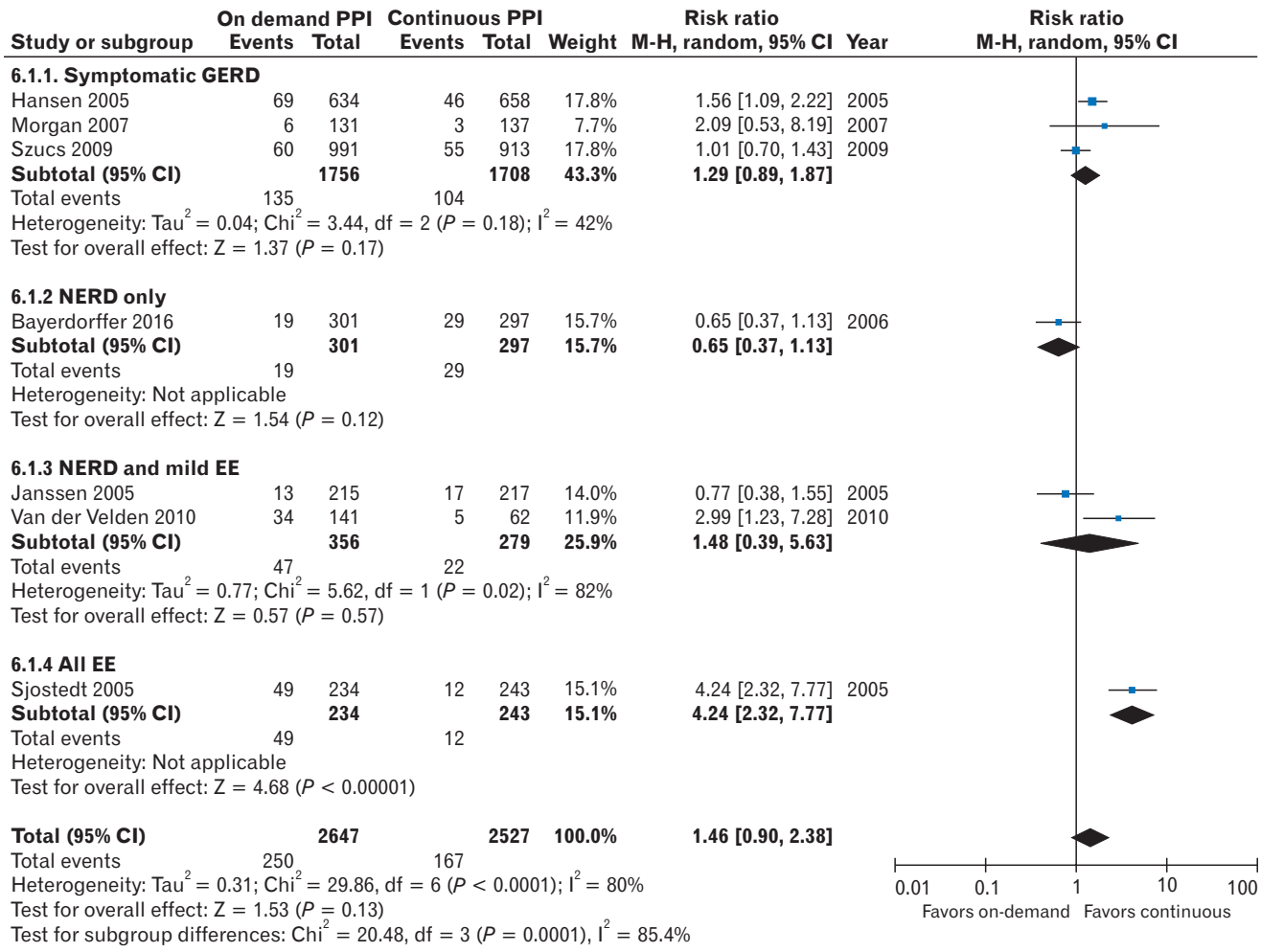
Test for overall effect: Z = 3.04 ($P = 0.002$)



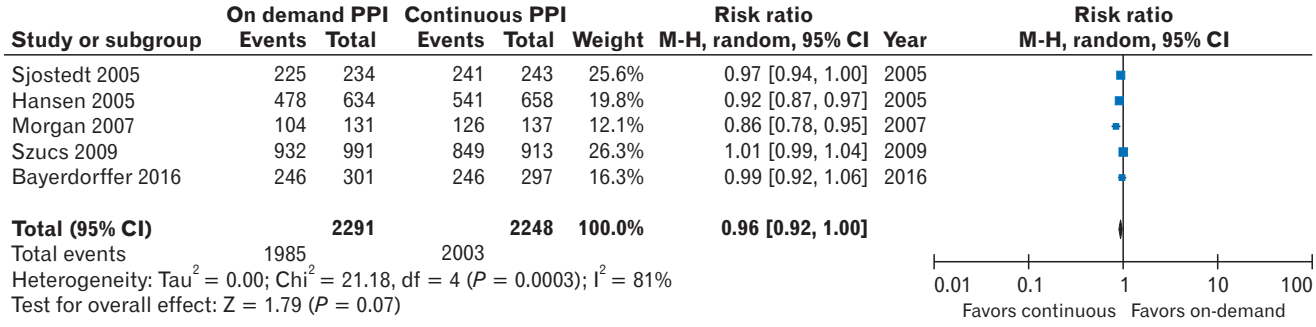
Supplementary Figure 13. Forest plot of symptom relief in subjects on esomeprazole 40 mg per day and other standard dose proton pump inhibitors at 8 weeks. M-H, Mantel-Haenszel.



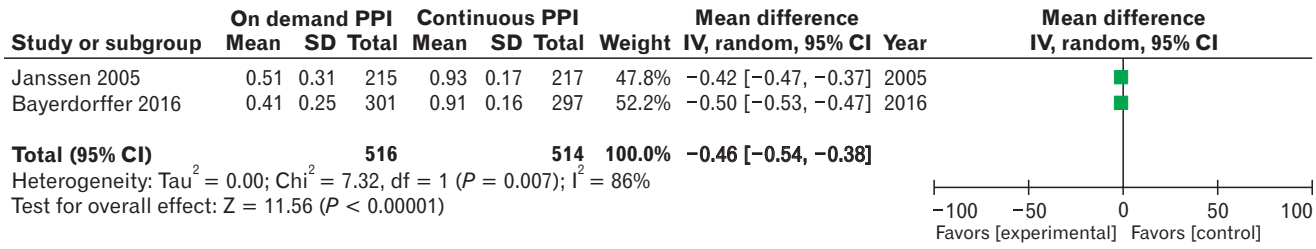
Supplementary Figure 14. Forest plot of risk ratios of failure between on-demand proton pump inhibitor (PPI) and continuous PPI groups in long-term management. M-H, Mantel-Haenszel.



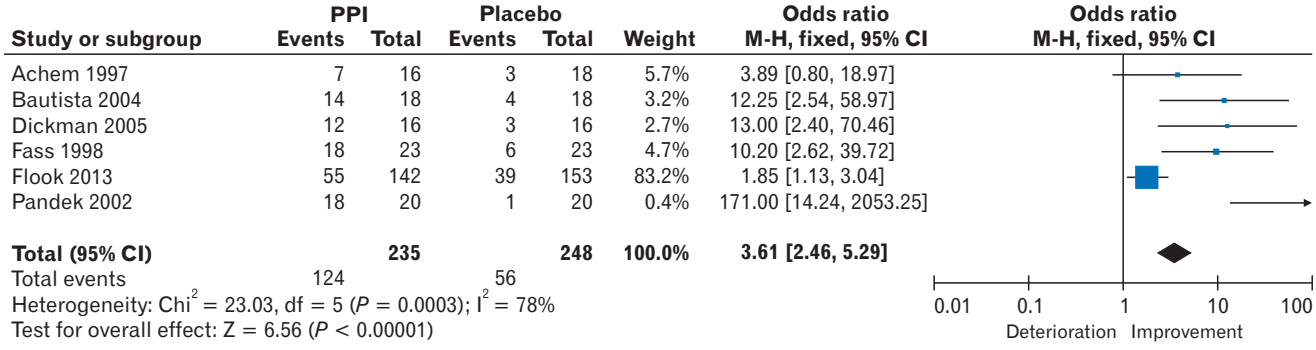
Supplementary Figure 15. Forest plot of risk ratios of failure between on-demand proton pump inhibitor (PPI) and continuous PPI groups in long-term management according to each subgroup analysis. GERD, gastroesophageal reflux disease; NERD, non-erosive reflux disease; EE, erosive esophagitis. M-H, Mantel-Haenszel.



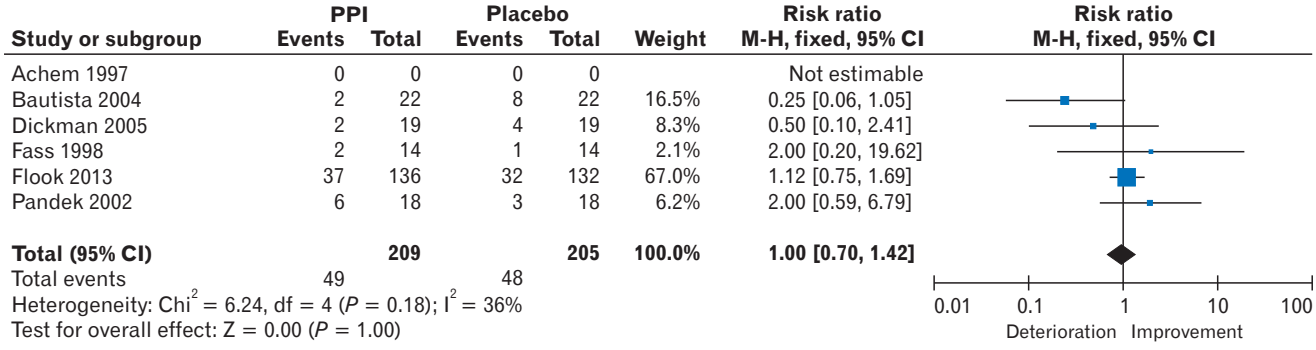
Supplementary Figure 16. Forest plot of the satisfaction between the on-demand proton pump inhibitor (PPI) and continuous PPI groups in long-term management. M-H, Mantel-Haenszel.



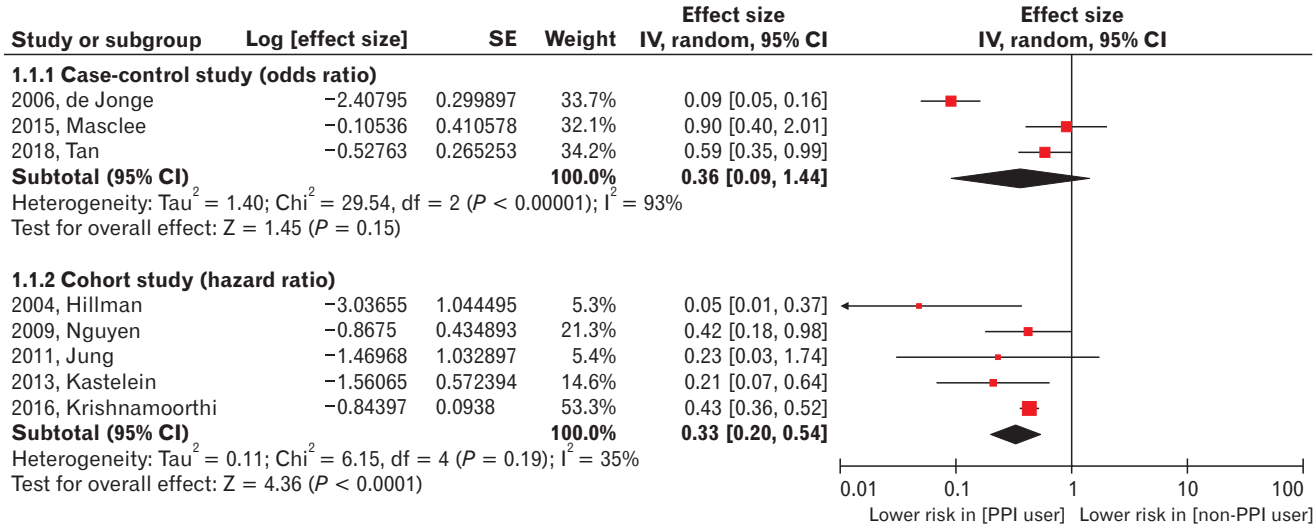
Supplementary Figure 17. Forest plot of medication use between on-demand proton pump inhibitor (PPI) and continuous PPI groups in long-term management.



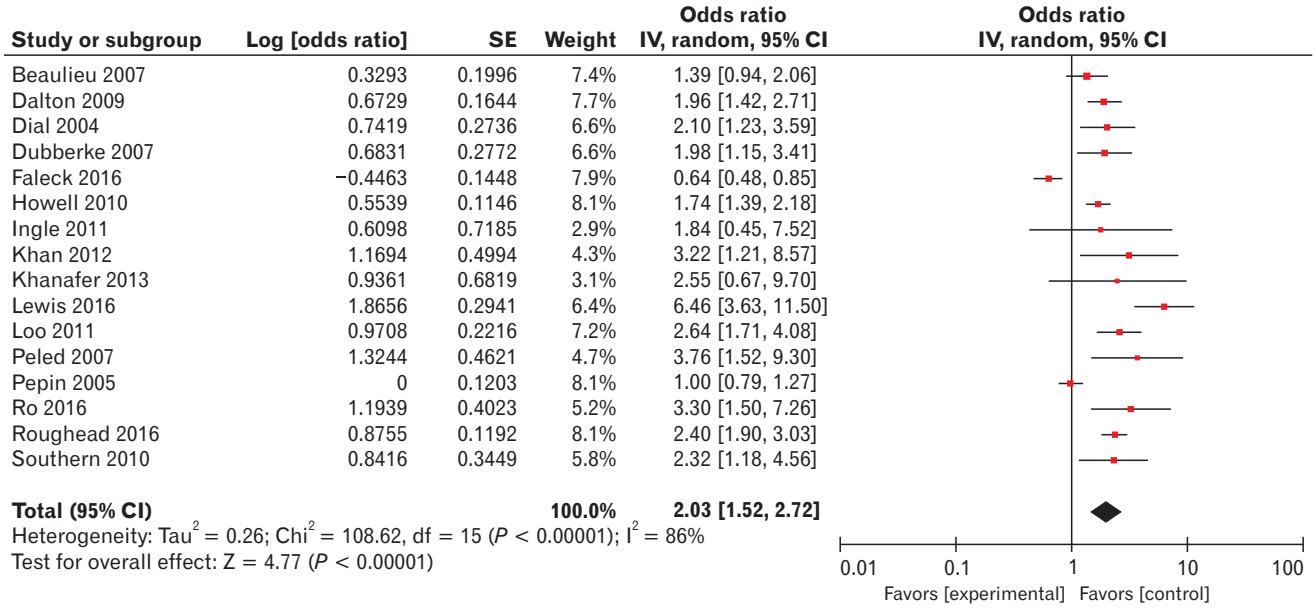
Supplementary Figure 18. Forest plot of the benefits from the proton pump inhibitor (PPI) treatment in gastroesophageal reflux disease positive patients with non-cardiac chest pain. M-H, Mantel-Haenszel.



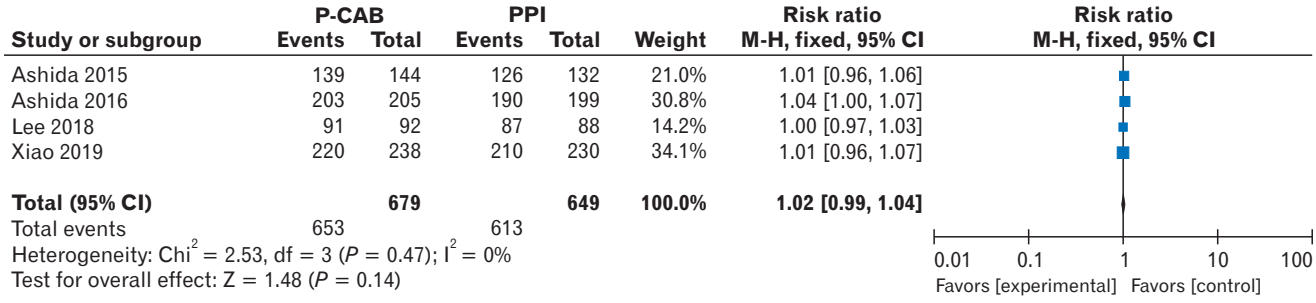
Supplementary Figure 19. Forest plot of the benefits from the proton pump inhibitor (PPI) treatment in gastroesophageal reflux disease negative patients with non-cardiac chest pain. M-H, Mantel-Haenszel.



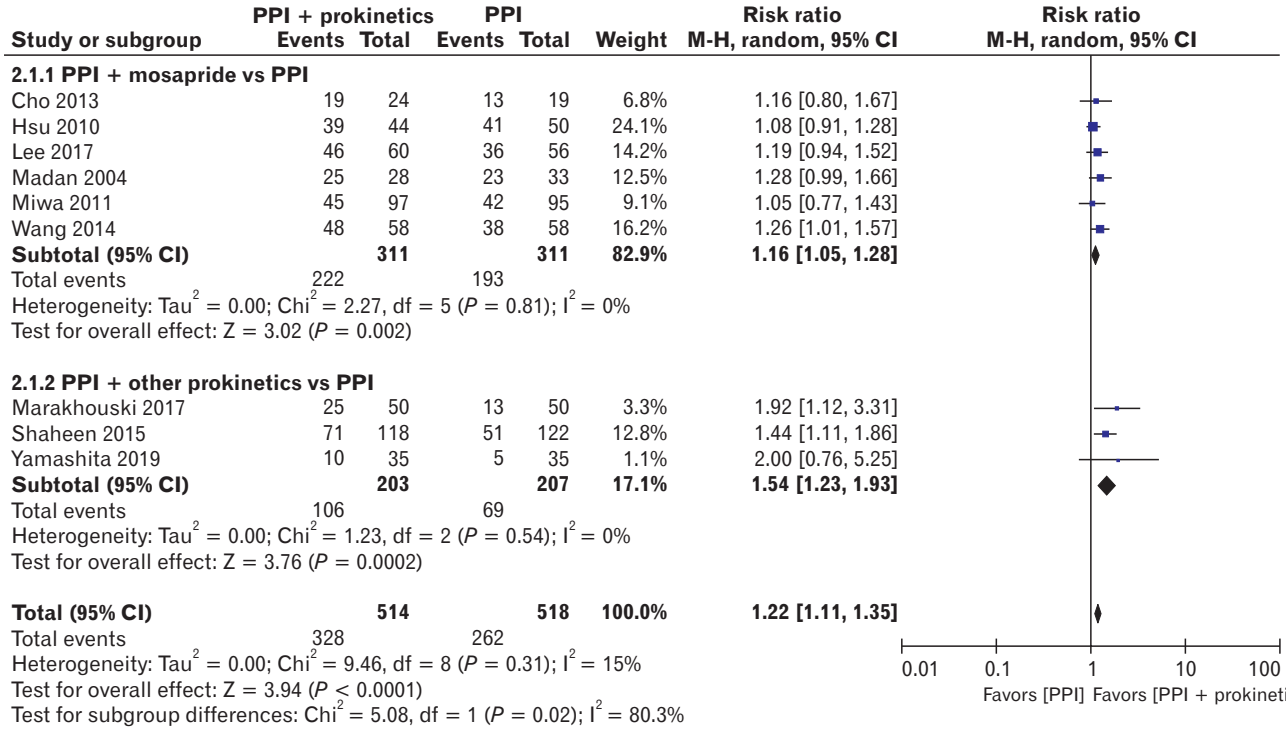
Supplementary Figure 20. Forest plot of the odds ratio of proton pump inhibitor (PPI) medication in the risk of progression into high-grade dysplasia or adenocarcinoma.



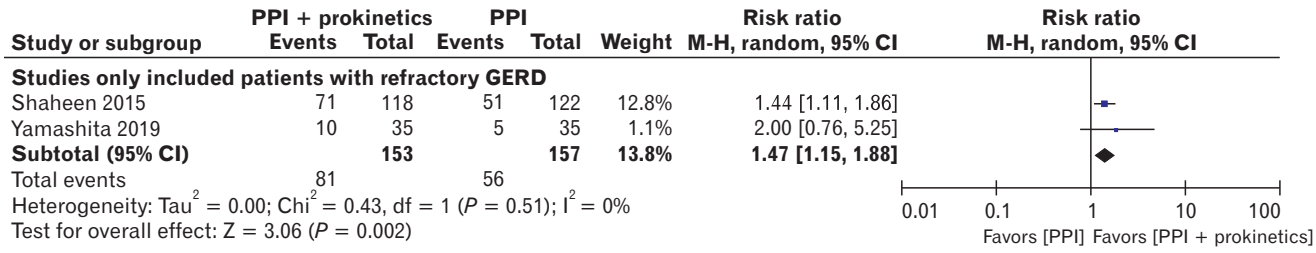
Supplementary Figure 21. Forest plot of the odds ratio of proton pump inhibitor medication in the risk of *Clostridium difficile* infection.



Supplementary Figure 22. Forest plot of the risk ratio of potassium-competitive acid blockers (P-CABs) in erosive esophagitis healing rates at 8 weeks. PPI, proton pump inhibitor. M-H, Mantel-Haenszel.



Supplementary Figure 23. Forest plot of the risk ratio of proton pump inhibitor (PPI) plus prokinetics treatment in reducing global symptoms of gastroesophageal reflux disease. M-H, Mantel-Haenszel.



Supplementary Figure 24. Forest plot of the risk ratio of proton pump inhibitor (PPI) plus prokinetics treatment in reducing global symptoms of refractory gastroesophageal reflux disease. M-H, Mantel-Haenszel.