Supplementary appendix

eAppendix A. Search strategies

Search strategy of Pubmed

#1 (COPD OR COAD OR COBD OR AECOPD OR emphysema OR "Chronic Obstructive Airway Disease" OR "Chronic obstructive pulmonary disease")

#2 (muscarinic OR LAMA OR tiotropium OR Spiriva OR glycopyrronium OR NVA237 OR Seebri OR umeclidinium OR GSK573719 OR Incruse OR aclidinium OR LAS34273 OR Turdorza OR Eklira)

#3 ((long* NEAR beta* NEAR agonist*) OR LABA OR salmeterol OR *formoterol OR indacaterol OR QAB149 OR vilanterol OR GW642444 OR olodaterol)

#4 ((inhal* NEAR corticosteroid*) OR ICS OR fluticasone OR budesonide OR beclomethasone OR ciclesonide OR flunisolid OR mometasone OR triamcinolone)

#5 (Ultibro OR QVA149 OR Stiolto OR Anoro)

#6 (Symbicort OR Viani OR Seretide OR Advair OR Atmadisc OR Adoair OR Foster OR Fostair OR Inuvair ORDulera OR Flutiform OR Breo)

#7 #1 AND ((#2 AND #3 AND #4) OR (#2 AND #6) OR (#4 AND #5))

This strategy is adapted to identify trials in other electronic databases

eTable 1 Patient inclusion criteria of included trials

Study	Inclusion criteria
Aaron 2007	● At least 1 exacerbation of COPD that required treatment with systemic steroids or antibiotics within the 12 months before randomisation; ● Age older than 35 years; ● History of 10 or more pack-years of cigarette smoking; ● Documented chronic airflow obstruction, with an FEV1/FVC ratio < 0.70 and a post-bronchodilator FEV1 < 65% of predicted value
Bremner 2018	● Aged ≥40 years with COPD and who were current/ former smokers with a ≥ 10-pack-year smoking history were eligible for enrollment ● COPD Assessment Test™ (CAT) score ≥ 10; ● A post-albuterol/salbutamol FEV1/FVC ratio < 0.70; ● A post-bronchodilator FEV1 < 50% of predicted and ≥1 moderate/severe exacerbation in the previous 12 months or a post-bronchodilator FEV1 ≥ 50% to < 80% of predicted and ≥2 moderate exacerbations or ≥1 severe exacerbation requiring hospitalization in the previous 12 months.
Cazzola 2007	● 50 years of age or older ● current or former smokers with a 20 pack-year or more history. ● baseline FEV1 of less than 50% of predicted, and a post-bronchodilator FEV1/ FVCless than70%
Frith 2015	● 40 years of age or older with Moderate to Severe COPD (Stage II or Stage III) according to the GOLD 2010 guideline ● Current or ex-smokers who have a smoking history of at least 10 pack years ● Qualifying FEV1 at Visit 2 (day -7)
Hoshino 2011	● post-bronchodilator FEV1/FVC < 0.7 ● a smoking history of >10 pack-years, and no history of asthma, or atopy as defined by a positive skin prick test to one or more common allergens.
Hoshino 2013	● >40 years of age with a diagnosis of COPD, ● a cigarette smoking history >10 pack-years, ● a postbronchodilator FEV 1 <70% of the predicted value and ratio of FEV 1 to forced vital capacity (FVC) <0.70.
Hanania 2012	● 40 years of age or older with COPD diagnosis ● At least 10 pack year smoking history ● Post-albuterol FEV1 greater than or equal to 40% to less than or equal to 80% of predicted normal ● An FEV1/FVC ratio of less than or equal to 0.70
Jung 2012	● Had a postbronchodilator FEV1/FVC ratio of less than 0.70 and FEV1 of less than 65% of the predicted value in the past 1 year or at screening; ● 40-80 years of age and had a smoking history of at least 10 pack-years.
Lee 2016	● Aged ≥40 years; ● A diagnosis of COPD with symptoms for >2 years; ● A history of ≥1 COPD exacerbation requiring a course of oral steroids and/or antibiotics within 1–12 months;

	● A current or prior smoking history of ≥10 pack-years; ● Pre-bronchodilator FEV1 ≤ 50% of predicted normal; ● Pre-bronchodilator FEV1/FVC <70%.
Lipson 2017	● Aged ≥ 40 years defined as GOLD Group D ● FEV1 < 50% and COPD Assessment is Test TM ≥ 10, ● Patients with FEV1 ≥ 50–< 80% and COPD Assessment Test TM ≥ 10, and either ≥ 2 moderate exacerbations in the past year or ≥ 1 severe exacerbation in the past year.
Lipson 2018	● 40 years of age or older and had symptomatic COPD ● Have either a FEV1< 50% of the predicted normal value and a history of at least one moderate or severe exacerbation in the previous year, or an FEV1 of 50 to 80% of the predicted normal value and at least two moderate exacerbations or one severe exacerbation in the previous year.
Maltais 2013	● aged o40 years and had a documented clinical history of COPD. ● FEV1 post-albuterol/salbutamol at least 30 to no more than 80% of predicted normal and FEV1/FVC ratio post-albuterol/salbutamol of no more than 0.70 ● A history of smoking at least 10 pack-yr is required.
Papi 2018	● Male and female ≥ 40 years ● Severe or very severe COPD diagnosed for at least 12 months ● Current smokers or ex-smokers who quit smoking at least 6 months prior to screening visit, with a smoking history of at least 10 pack years Post-bronchodilator FEV1 < 50% of the predicted normal value and a post-bronchodilator FEV1/FVC ratio < 0.7 ● Documented history of at least one exacerbation in the 12 months ● Patient under double therapy for at least 2 months prior to screening. Double therapy will be defined by treatment with any of the following: Orally inhaled corticosteroid (ICS) and (long-acting beta2-agonist) LABA ICS and long-acting muscarinic antagonist (LAMA) Orally LABA and LAMA monotherapy with LAMA for at least 2 months prior to screening ● Symptomatic patient at screening with a CAT score ≥ 10. ● Cooperative attitude and ability to use correctly the inhalers, the spacer AeroChamber Plus (only to patients who are using a spacer), the electronic devices with COPD questionnaire.
Siler 2015-S	● 40 years of age or older had an established history of COPD; ● Current or former cigarette smoker with a smoking history of 10 pack-years or more; ● A pre- and post-salbutamol (albuterol) FEV 1 /FVC < 0.70 and a post-albuterol FEV 1 of 70% of predicted normal values or less ; ● A score of 2 or higher on the modifi ed Medical Research Council Dyspnea Scale at study Visit 1.
Siler 2015-V	● 40 years of age or older had an established history of COPD; ● Current or former cigarette smoker with a smoking history of 10 pack-years or more; ● A pre- and post-salbutamol (albuterol) FEV 1 /FVC < 0.70 and a post-albuterol FEV 1 of 70% of predicted normal values or less ; ● A score of 2 or higher
Singh 2016	● Male or female adults aged ≥ 40 years with a diagnosis of COPD ● Current smokers or ex-smokers ● A post-bronchodilator FEV1 < 50% of the predicted normal value and a post-

	bronchodilator FEV1/FVC < 0.7 ● At least one exacerbation in the 12 months preceding the screening visit
Sousa 2016	● 40 years of age or older with an established clinical history of COPD, ● Current or former smokers with ≥10 pack-years smoking history, ● Had a pre- and post-albuterol/salbutamol FEV1/FVC ratio of < 0.7 and a pre- and post-albuterol/salbutamol FEV1 of <70% of predicted normal values. ● Had a dyspnoea score of ≥2 on the modified Medical Research Council Dyspnoea Scale16 at Visit 1
Vestbo 2017	● Male and female COPD patients aged ≥ 40 years ● Current smokers or ex-smokers ● FEV1<50% predicted (FEV1/FVC <0.7) ● At least 1 documented exacerbations in the last 12 Mo
Welte 2009	● >=40 years of age, diagnosed COPD with symptoms >=2 years, pre-bronchodilatory FEV1 <=50% of predicted normal values

eTable 2 Reasons for studies excluded after full-text review

Study	Reason for exclusion
Andò 2008	Not reporting triple therapy
Bateman 2008	Not reporting triple therapy
Bölükbas 2011	Duration less than 4 weeks
Covelli H 2015	Not reporting triple therapy
Fang 2008	Not English article
Ferroni 2016	Not randomized trial
Magnussen 2012	Not reporting triple therapy
Mittmann 2011	Duplicate publication; No interesting outcomes
Nielsen 2013	Duplicate publication; No interesting outcomes
Pasqua 2010	No interesting outcomes
Perng 2006	Not randomized trial
Perng 2009	Not reporting triple therapy
Rabe 2008	Not reporting triple therapy
Roisman 2007	Not English article
Saito 2015	No interesting outcomes
Samp 2017	Not randomized trial
Saraç 2016	Not reporting triple therapy
Short 2012	Not randomized trial
Siler 2016	Duplicate publication
Singh 2008	Duration less than 4 weeks
Singh 2017	Not randomized trial
Trudo 2015	Not randomized trial
Vogelmeier 2013	Not reporting triple therapy
Wedzicha 2008	Not reporting triple therapy
Wedzicha 2016	Not reporting triple therapy
Williamson 2010	No interesting outcomes

Studies excluded after full-text review

1 Andò F, Ruggeri P, Girbino G, et al. Tiotropium and salmeterol/fluticasone combination do not cause oxygen desaturation in COPD. Respir Med 2008;102(6):815-8.

2 Bateman ED, van Dyk M, Sagriotis A. Comparable spirometric efficacy of tiotropium compared with salmeterol plus fluticasone in patients with COPD: A pilot study. Pulm Pharmacol Ther 2008;21(1):20-5.

3 Bölükbas S, Eberlein M, Eckhoff J, et al. Short-term effects of inhalative tiotropium/formoterol/budenoside versus tiotropium/formoterol in patients with newly diagnosed chronic obstructive pulmonary disease requiring surgery for lung cancer: a prospective randomized trial. Eur J Cardiothorac Surg 2011;39(6):995-1000.

4 Covelli H, Pek B, Schenkenberger I, et al. Efficacy and safety of fluticasone furoate/vilanterol or tiotropium in subjects with COPD at cardiovascular risk. Int J Chron Obstruct Pulmon Dis 2015;11:1-12.

5 Fang LZ, Liang X, Zhang JQ, et al. Combination of inhaled salmeterol/fluticasone and tiotropium in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Zhonghua Jie He He Hu Xi Za Zhi 2008;31(11):811-4.

6 Ferroni E, Belleudi V, Cascini S, et al. Role of Tiotropium in Reducing Exacerbations of Chronic Obstructive Pulmonary Disease When Combined With Long-Acting β2 -Agonists and Inhaled Corticosteroids: The OUTPUL Study. J Clin Pharmacol 2016 ;56(11):1423-1432.

7 Magnussen H, Paggiaro P, Schmidt H, et al. Effect of combination treatment on lung volumes and exercise endurance time in COPD. Respir Med 2012;106(10):1413-20.

8 Mittmann N, Hernandez P, Mellström C, et al. Cost effectiveness of budesonide/formoterol added to tiotropium bromide versus placebo added to tiotropium bromide in patients with chronic obstructive pulmonary disease: Australian, Canadian and Swedish healthcare perspectives. Pharmacoeconomics 2011;29(5):403-14.

9 Nielsen R, Kankaanranta H, Bjermer L, Lange P, Arnetorp S, Hedegaard M, Stenling A, Mittmann N. Cost effectiveness of adding budesonide/formoterol to tiotropium in COPD in four Nordic countries. Respir Med 2013;107(11):1709-21.

10 Pasqua F, Biscione G, Crigna G, et al. Combining triple therapy and pulmonary rehabilitation in patients with advanced COPD: a pilot study. Respir Med 2010;104(3):412-7.

11 Perng DW, Wu CC, Su KC, et al. Additive benefits of tiotropium in COPD patients treated with long-acting b2 agonists and corticosteroids. Respirology 2006;11(5):598-602.

12 Perng DW, Tao CW, Su KC, et al. Anti-inflammatory effects of salmeterol/ fluticasone, tiotropium/ fluticasone or tiotropium in COPD. Eur Respir J 2009;33(4):778-84.

13 Rabe KF, Timmer W, Sagkriotis A, et al. Comparison of a combination of tiotropium plus formoterol to salmeterol plus fluticasone in moderate COPD. Chest 2008;134(2):255-262.

14 Roisman G. Tiotropium in combination with placebo, salmeterol, or fluticasone- salmeterol for treatment of chronic obstructive pulmonary disease. A randomized trial. Revue de Pneumologie Clinique 2007; 63:390-391

15 Saito T, Takeda A, Hashimoto K, et al. Triple therapy with salmeterol/fluticasone propionate 50/250 plus tiotropium bromide improve lung function versus individual treatments in moderate-to-severe Japanese COPD patients: a randomized controlled trial - Evaluation of Airway sGaw after treatment with tripLE. Int J Chron Obstruct Pulmon Dis 2015;10:2393-404.

16 Samp JC, Joo MJ, Schumock GT, et al. Comparative Effectiveness of Long-Acting Beta2 -Agonist Combined with a Long-Acting Muscarinic Antagonist or Inhaled Corticosteroid in Chronic Obstructive Pulmonary Disease. Pharmacotherapy 2017;37(4):447-455.

17 Saraç P, Sayıner A. Compare the efficacy and safety of long-acting anticholinergic and a combination of inhaled steroids and long-acting beta-2 agonist in moderate chronic obstructive pulmonary disease. Tuberk Toraks 2016;64(2):112-8.

18 Short PM, Williamson PA, Elder DHJ, et al. The impact of tiotropium on mortality and exacerbations when added to inhaled corticosteroids and long-acting β-agonist therapy in COPD. Chest 2012;141(1):81-86.

19 Siler TM., Kerwin E, Tombs L, et al. Triple Therapy of Umeclidinium + Inhaled Corticosteroids/Long-Acting Beta2 Agonists for Patients with COPD: Pooled Results of Randomized Placebo-Controlled Trials. Pulm Ther 2016; 2:43-58.

20 Singh D, Brooks J, Hagan G, et al. Superiority of "triple" therapy with salmeterol/fluticasone propionate and tiotropium bromide versus individual components in moderate to severe COPD. Thorax 2008;63(7):592-8.

21 Singh D, Corradi M, Spinola M, et al. Triple therapy in COPD: new evidence with the extrafine fixed combination of beclomethasone dipropionate, formoterol fumarate, and glycopyrronium

bromide. Int J Chron Obstruct Pulmon Dis 2017;12:2917-2928.

22 Trudo F, Kern DM, Davis JR, et al. Comparative effectiveness of budesonide/formoterol combination and tiotropium bromide among COPD patients new to these controller treatments. Int J Chron Obstruct Pulmon Dis 2015;10:2055-66.

23 Vogelmeier CF, Bateman ED, Pallante J, et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. Lancet Respir Med 2013;1(1):51-60.

24 Wedzicha JA, Calverley PM, Seemungal TA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. 2008;177(1):19-26.

25 Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. N Engl J Med. 2016;374(23):2222-34.

26 Williamson PA, Short PM, Clearie KL, et al. Paradoxical trough effects of triple therapy with budesonide/formoterol and tiotropium bromide on pulmonary function outcomes in COPD. Chest. 2010;138(3):595-604.

eTable 3. Subgroup analysis by duration

Outcome	Reference	Effect Size (95% CI)	P value
Triple therapy vs ICS/LABA			
Duration ≥ 6 months			
Exacerbation rates per patients	3	0.77 (0.66, 0.91)	0.03
All cause death	3	0.95 (0.73, 1.23)	0.70
FEV1 trough, L	3	0.11 (0.06, 0.15)	0
AEs	3	0.98 (0.91, 1.07)	0.11
SAEs	3	0.74 (0.48, 1.15)	0.89
Cardiovascular	3	1.02 (0.91, 1.15)	0.75
Pneumonia	3	1.36 (0.86, 2.14)	0.19
SGRQ score		-1.83 (-2.47, -1.19)	0
Duration < 6 months			
All cause death	6	0.27 (0.09, 0.88)	0.03
FEV1 trough, L	9	0.12 (0.10, 0.13)	0
AEs	7	1.02 (0.99, 1.05)	0.68
SAEs	6	0.99 (0.87, 1.13)	0.19
Cardiovascular	5	0.65 (0.39, 1.06)	0.09
Pneumonia	6	0.80 (0.41, 1.57)	0.52
SGRQ score		-1.79 (-2.47, -1.12)	0
Triple therapy vs LAMA			
Duration ≥ 6 months			
Exacerbation rates per patients	2	0.80 (0.73, 0.89)	0
Severe exacerbations	2	0.62 (0.49, 0.87)	0
All cause death	2	0.74 (0.46, 1.18)	0.21
FEV1 trough, L	3	0.06 (0.04, 0.08)	0
AEs	2	1.05 (0.82, 1.34)	0.72
SAEs	2	0.85 (0.71, 1.02)	0.09
Pneumonia	2	1.44 (0.85, 2.45)	0.18
SGRQ score	3	-2.32(-3.81, -0.82)	0.02
Duration < 6 months			
Exacerbation rates per patients	3	0.58 (0.38, 0.87)	0.008
Severe exacerbations	2	0.33 (0.16, 0.67)	0.002
All cause death	2	0.46 (0.10, 2.04)	0.30
FEV1 trough, L	8	0.08 (0.06, 0.09)	0
AEs	4	1.02 (0.87, 1.19)	0.83
SAEs	4	0.77 (0.54, 1.09)	0.15
Pneumonia	2	0.61 (0.15, 2.54)	0.50
SGRQ score	5	-3.30 (-4.87, -1.73)	0

eTable 4. Subgroup analysis by eosinophil level (Descriptive analysis)

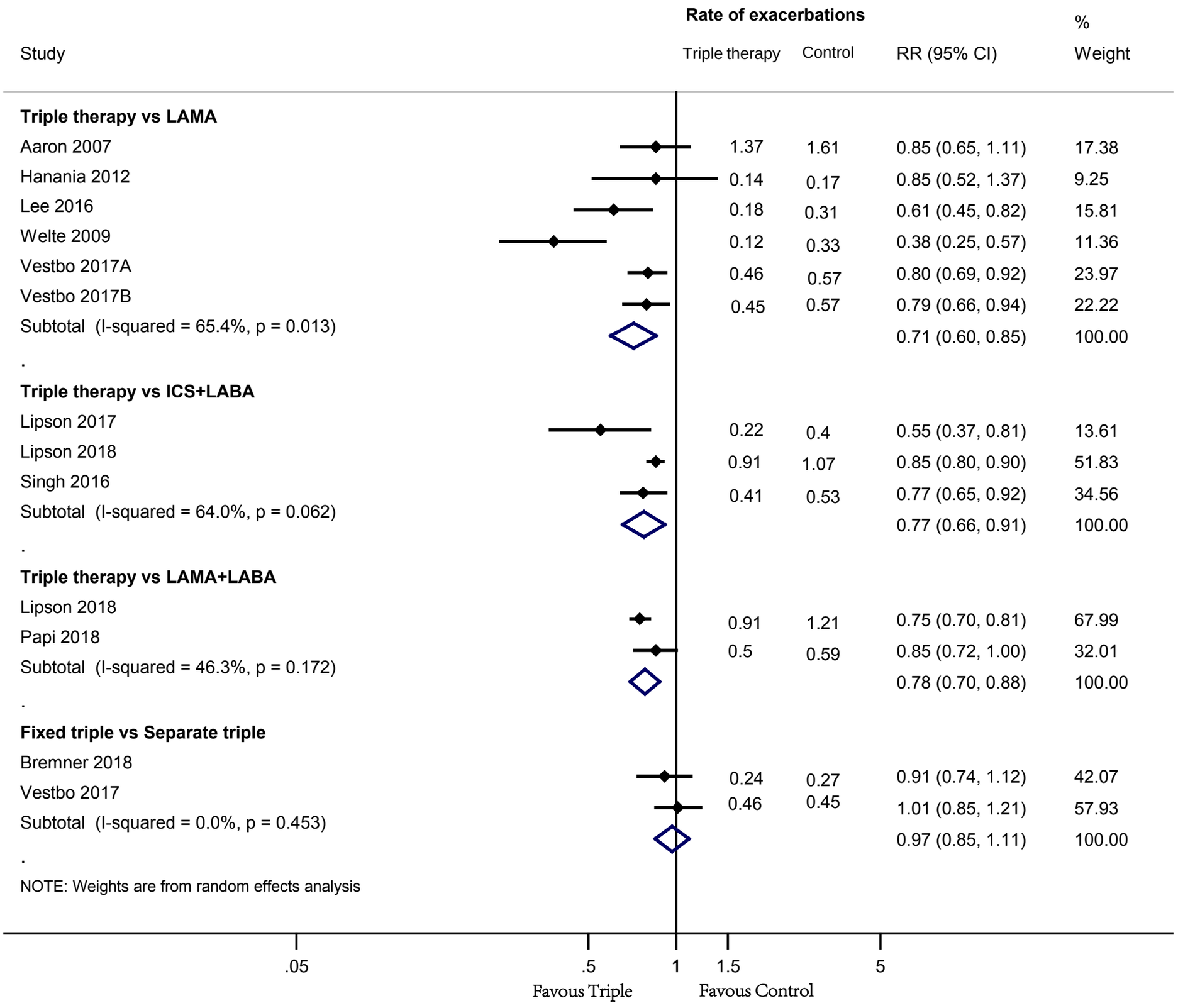
Study	Rate ratio of Moderate to severe exacerbations	
	Eosinophil level≥200 or 150 cells per microliter	Eosinophil level≤200 or 150 cells per microliter
Triple therapy vs LAMA		
Vestbo 2017 (fixed triple)	0.64 (0.51-0.81)	0.92 (0.77-1.10)
Vestbo 2017 (open triple)	0.62 (0.47-0.83)	0.91 (0.72-1.14)
Triple therapy vs LAMA+LABA		
Lipson 2018	Annual Rate: 0.95 vs 1.39	Annual Rate: 0.85 vs 0.97
Papi 2018	0.81(0.65-1.01)	0.87(0.69-1.10)
Triple therapy vs ICS+LABA		
Lipson 2018	Annual Rate: 0.95 vs 1.08	Annual Rate: 0.85 vs 1.06
Singh 2016	0.80(0.65-0.99)	0.72(0.52-1.00)

eTable 5. Sensitivity Analyses Removing Studies with High Risk of Bias

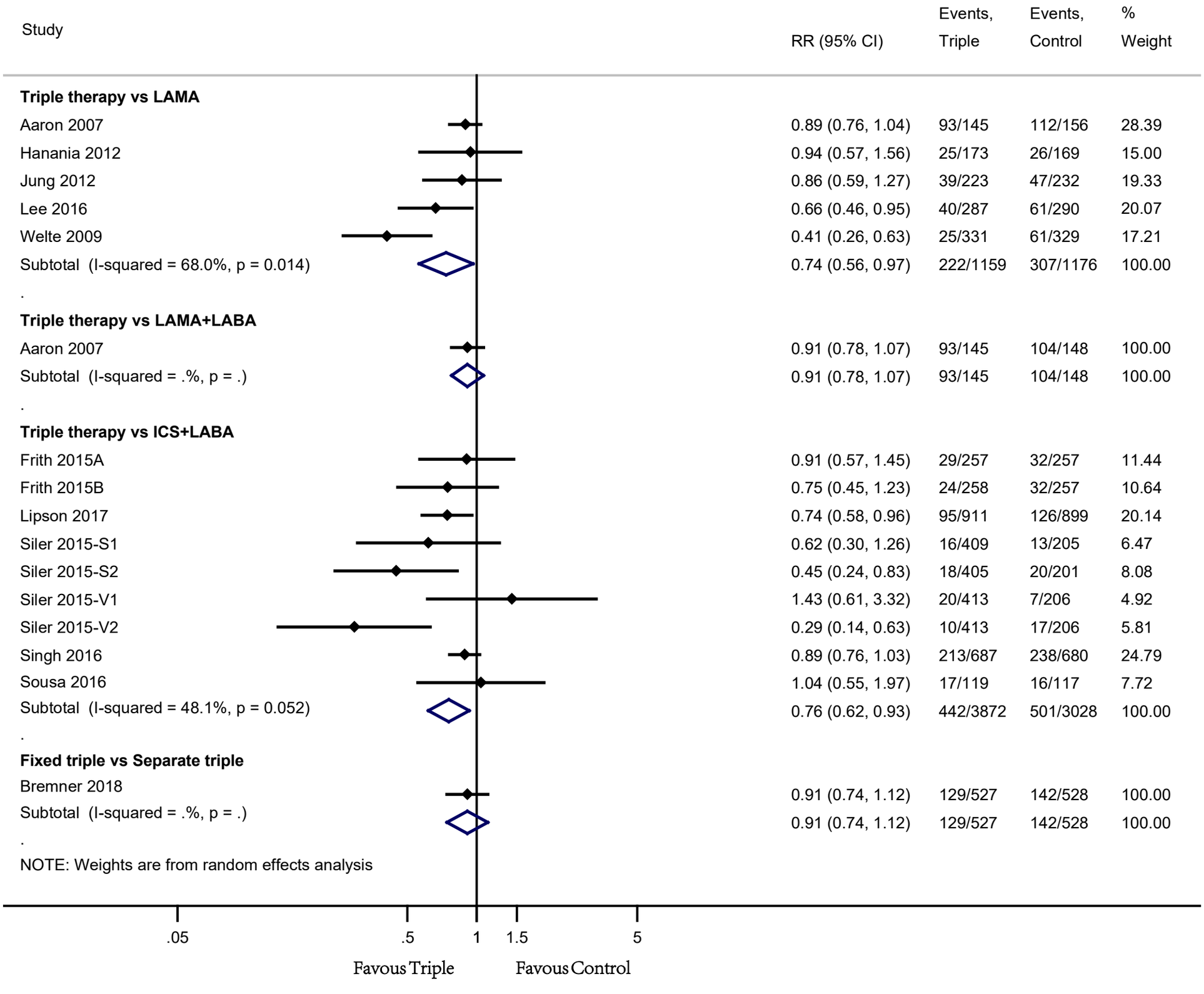
Outcomes	N. of trials	Effect Size (95% CI)	I^2 value	P value
Triple therapy vs LAMA				
Efficacy				
Exacerbation rates per patients	4	0.73 (0.60, 0.90)	67.5	0.002
Number of patients with 1 or more	3	0.79 (0.66, 0.94)	78.2	0.01
Time to first exacerbation	3	0.70 (0.53, 0.93)	78.1	0.014
Severe exacerbations	4	0.58 (0.47, 0.72)	0	0
All cause death	4	0.71 (0.45, 1.10)	23.3	0.125
FEV1 trough, L	6	0.07 (0.05, 0.08)	0	0
Safety				
AEs	5	0.99 (0.93, 1.05)	0	0.731
SAEs	4	0.82 (0.69, 0.98)	0	0.03
Cardiovascular	2	0.77 (0.45, 1.31)	0	0.331
Pneumonia	2	1.44 (0.85, 2.45)	0	0.18
Quality of life				
SGRQ score	4	-2.25 (-3.45, -1.05)	0	0

high risk of bias was defined according to the Cochrane Instrument

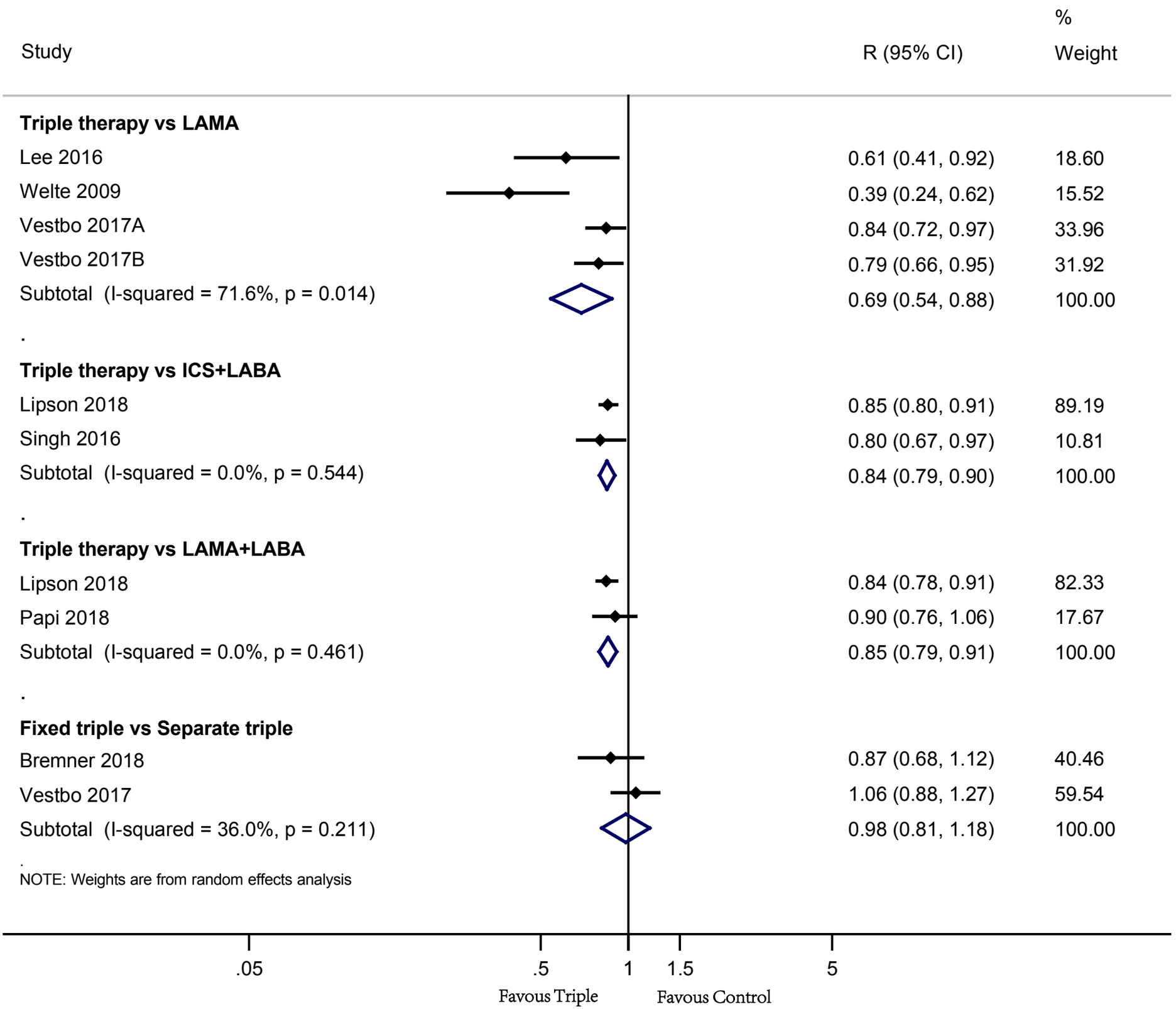
eFigure 1A Association of triple therapy with the rate of moderate or severe exacerbations



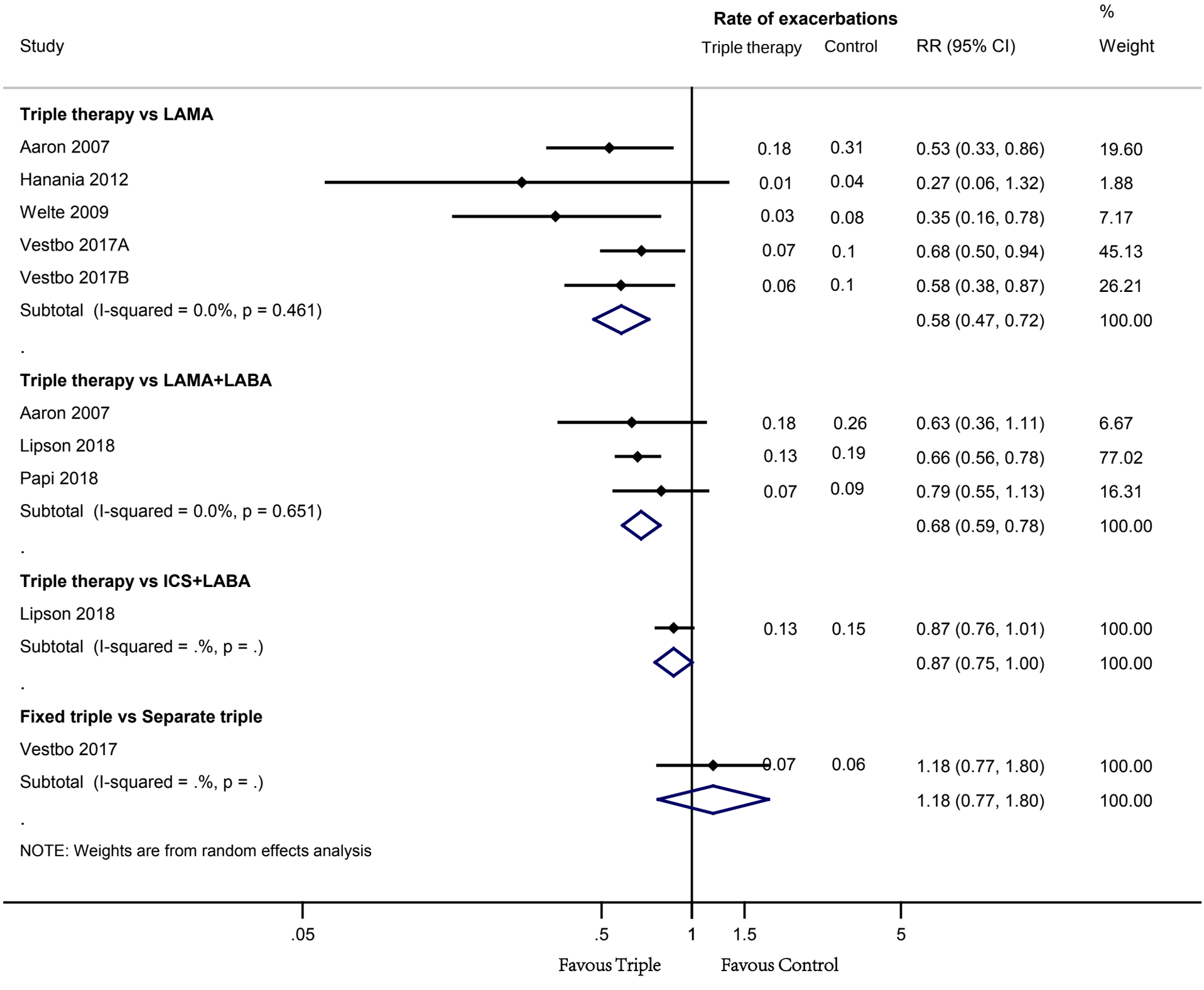
eFigure 1B Association of triple therapy with the number of patients with 1 or more moderate or severe exacerbations



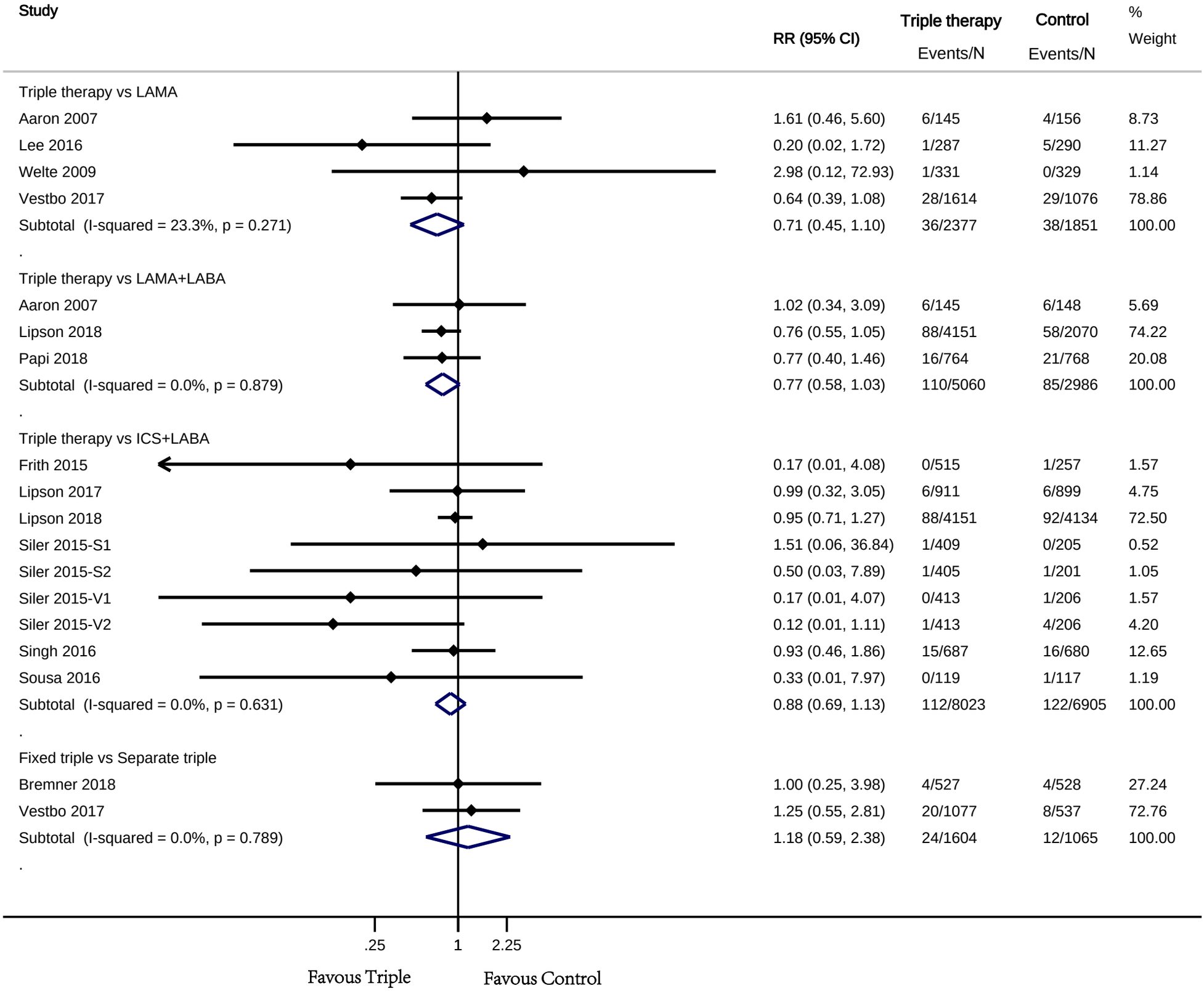
eFigure 1CAssociation of triple therapy with time to first moderate or severe exacerbations



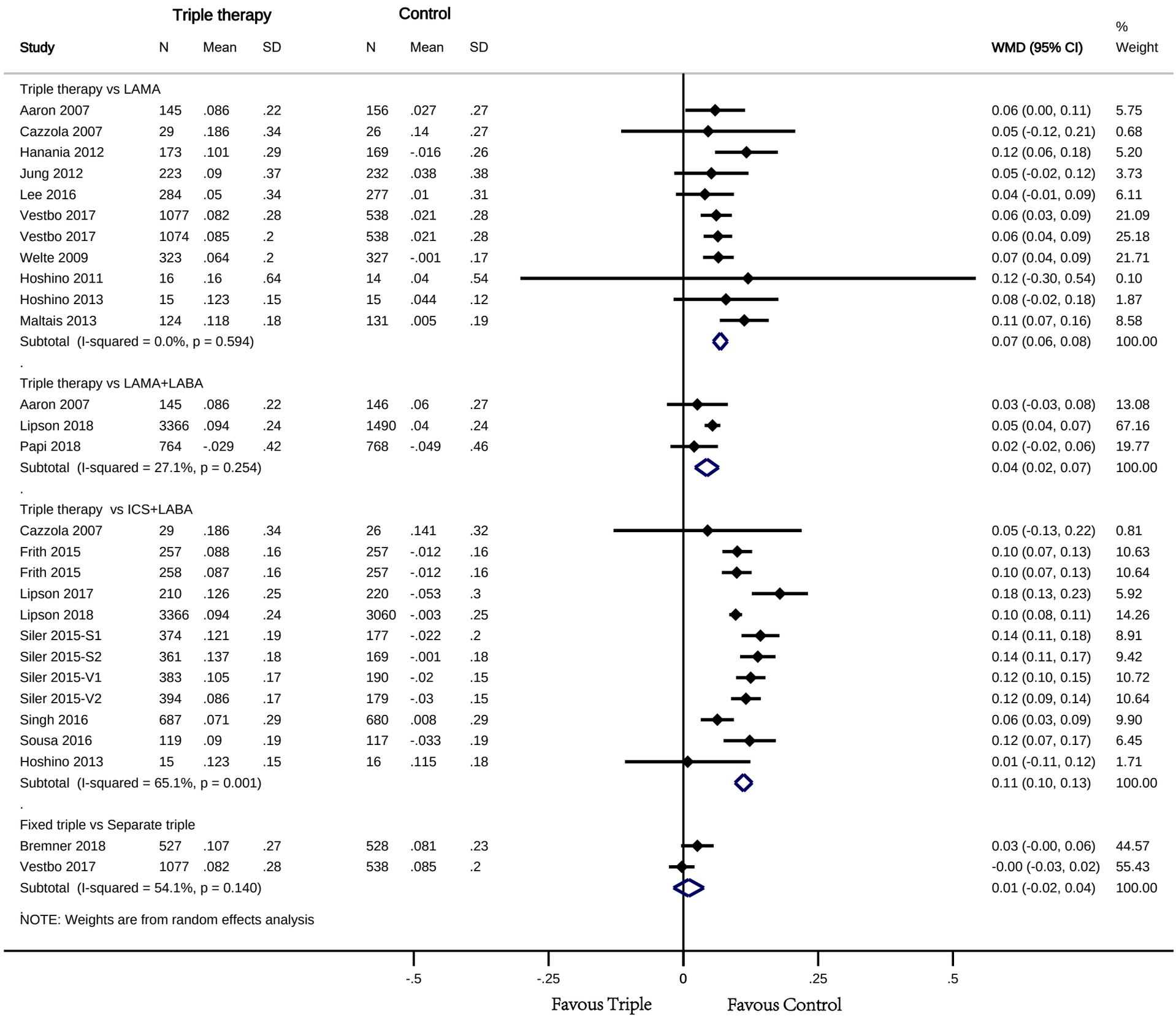
eFigure 2A Association of triple therapy with the rate of severe exacerbations



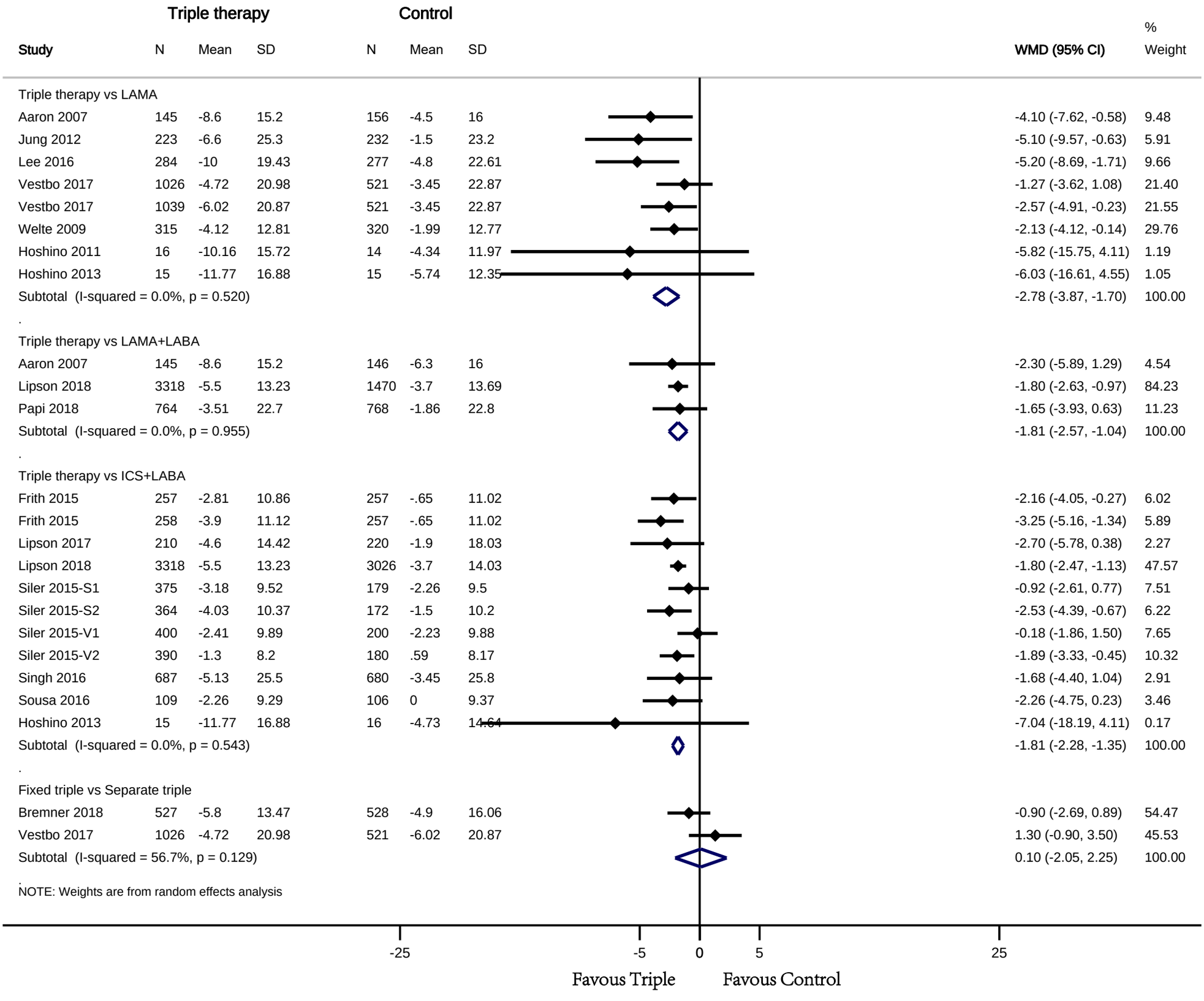
eFigure 2B Association of triple therapy with death from any cause



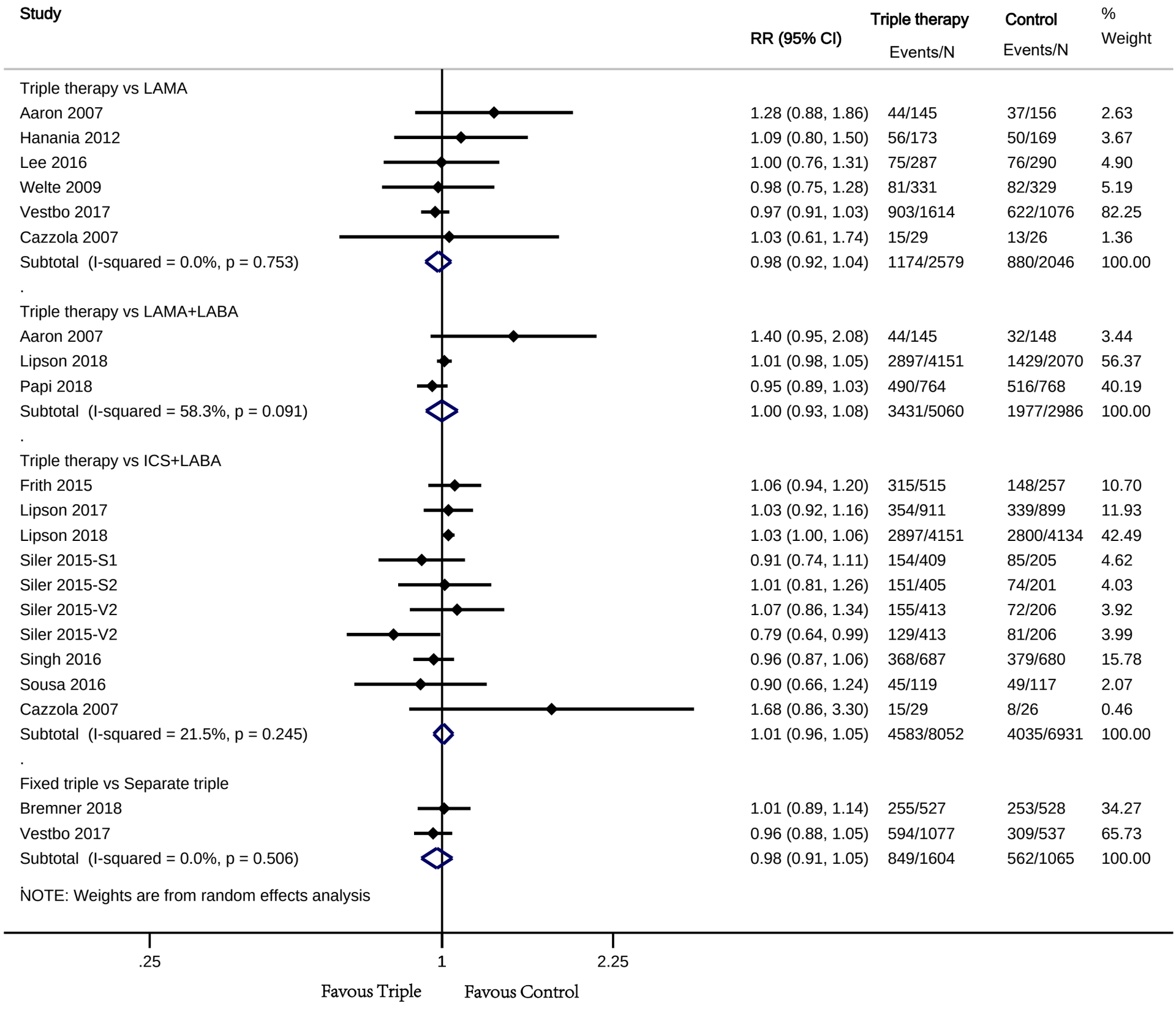
eFigure 2C Association of triple therapy with trough FEV1



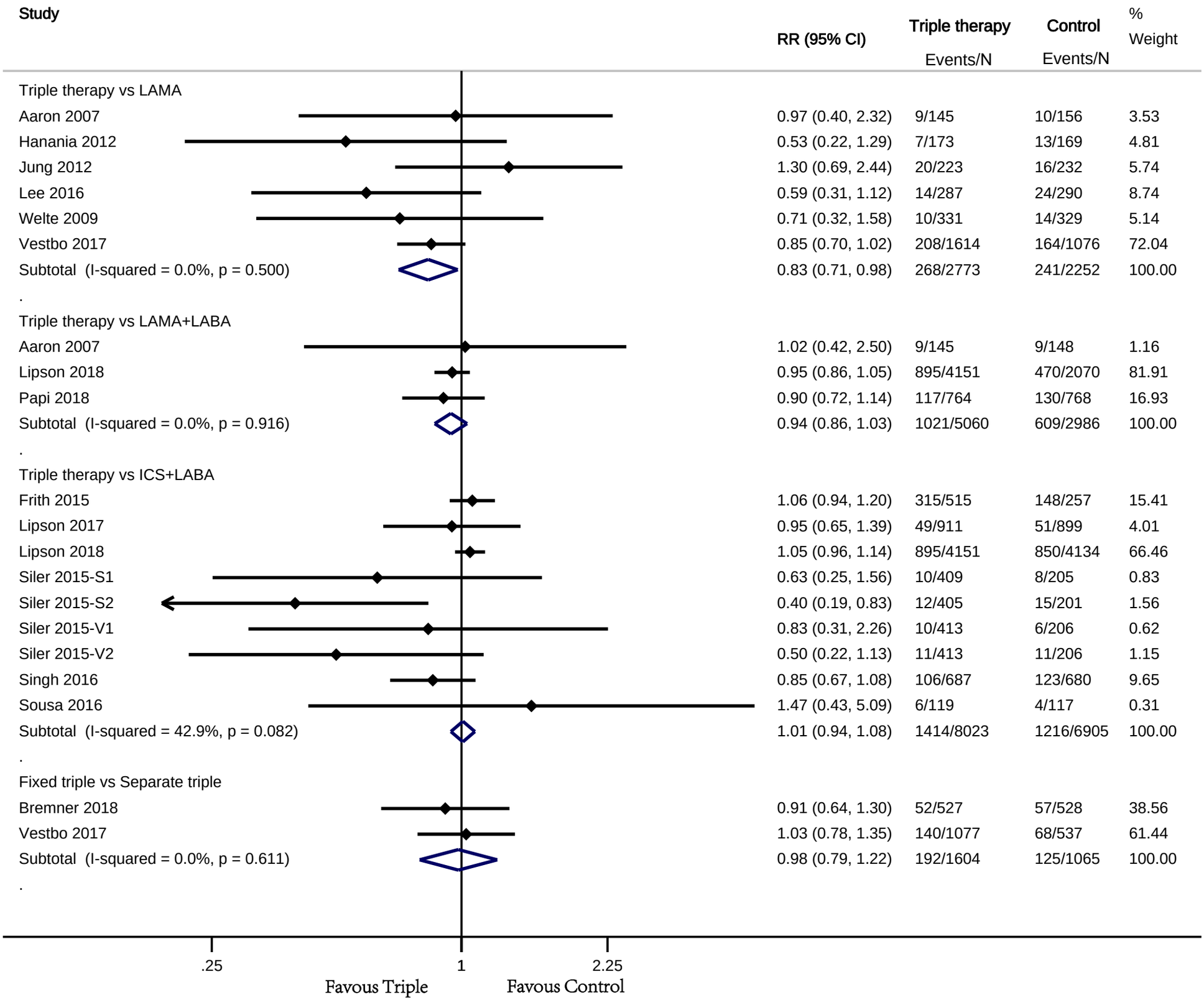
eFigure 2D Association of triple therapy with SGRQ score



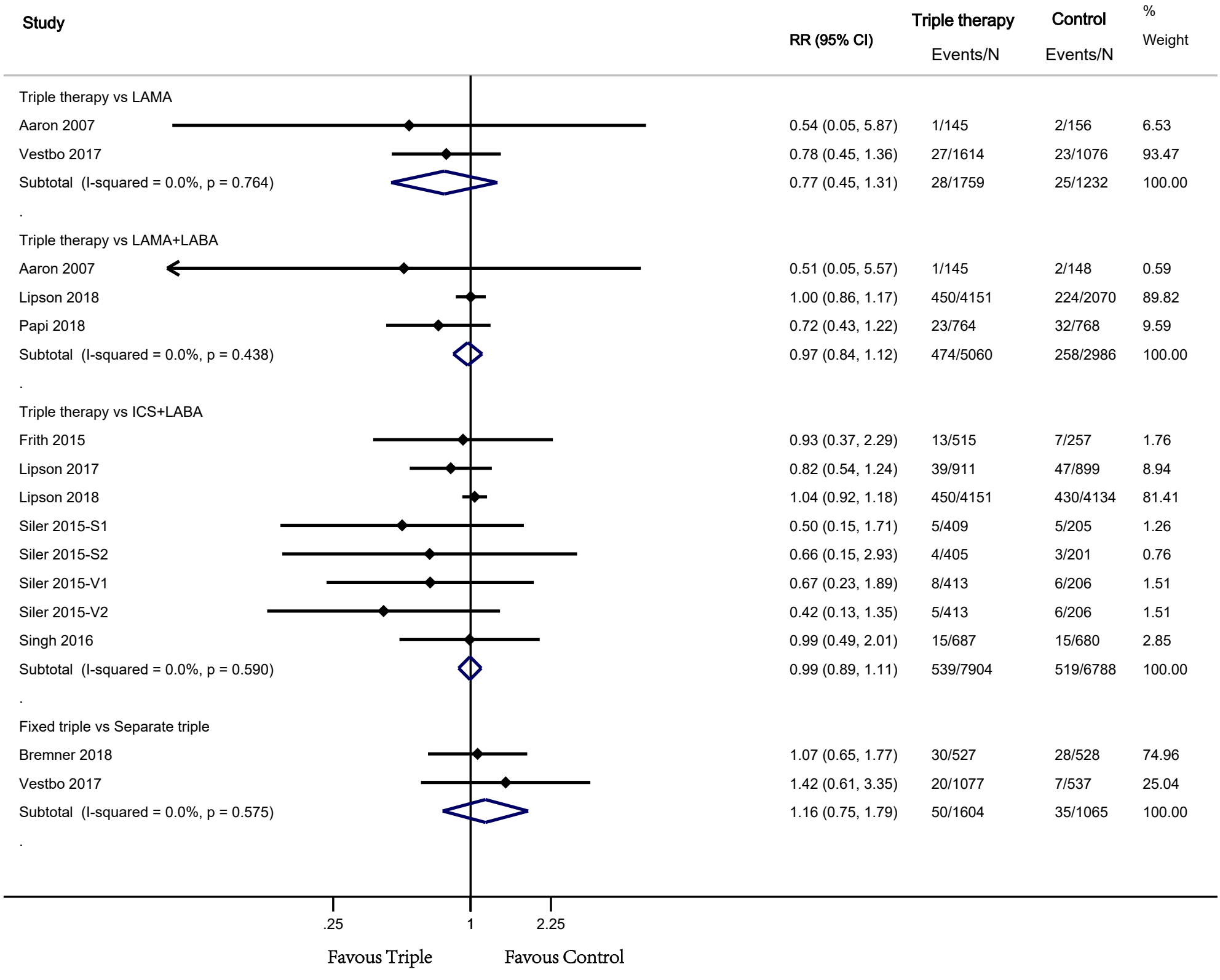
eFigure 3. Association of triple therapy with AEs



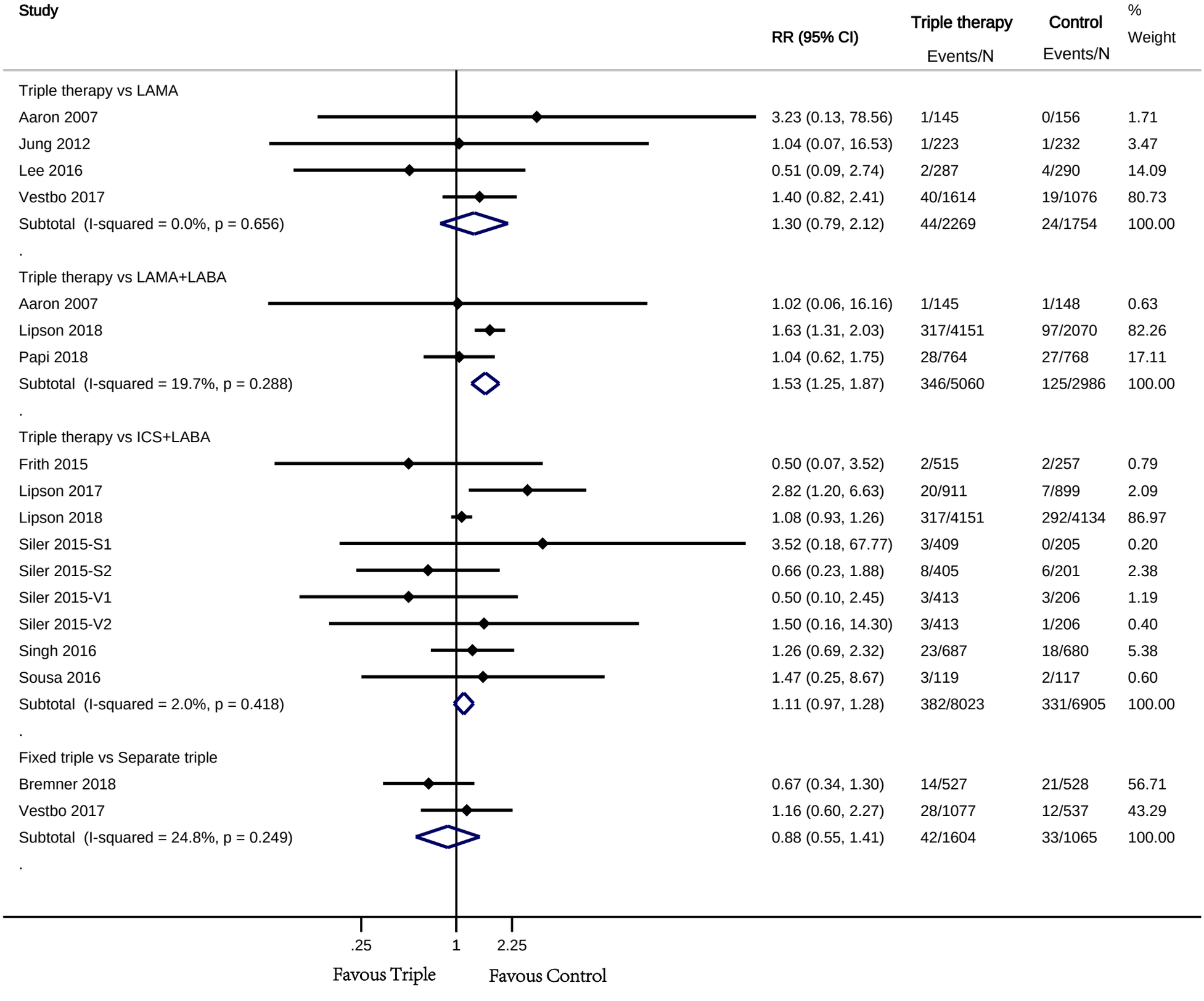
eFigure 4. Association of triple therapy with SAEs



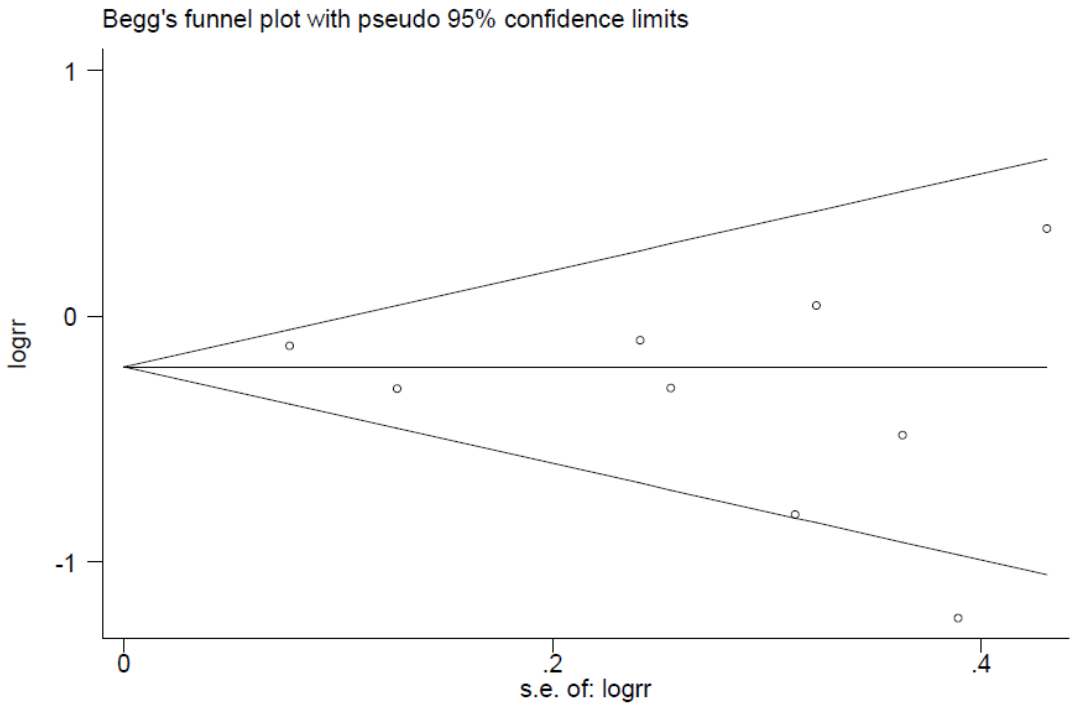
eFigure 5. Association of triple therapy with cardiovascular events



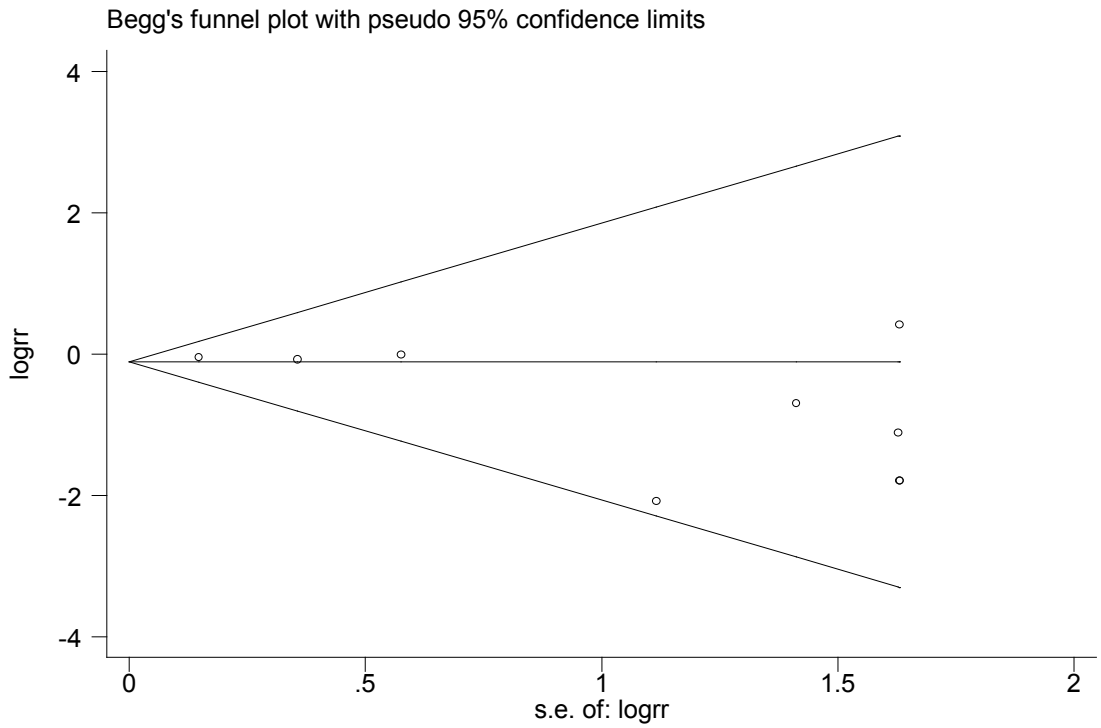
eFigure 6. Association of triple therapy with pneumonia events



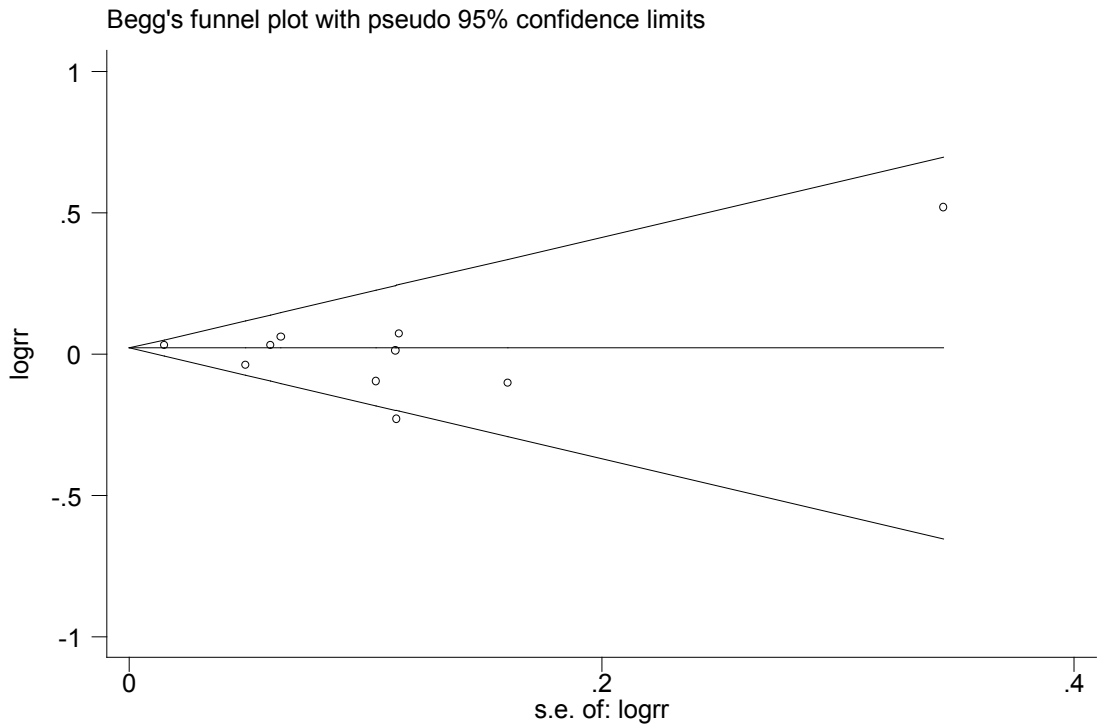
eFigure 7A. Funnel plot of the included studies: triple therapy vs ICS/LABA on the risk of moderate to severe exacerbations.



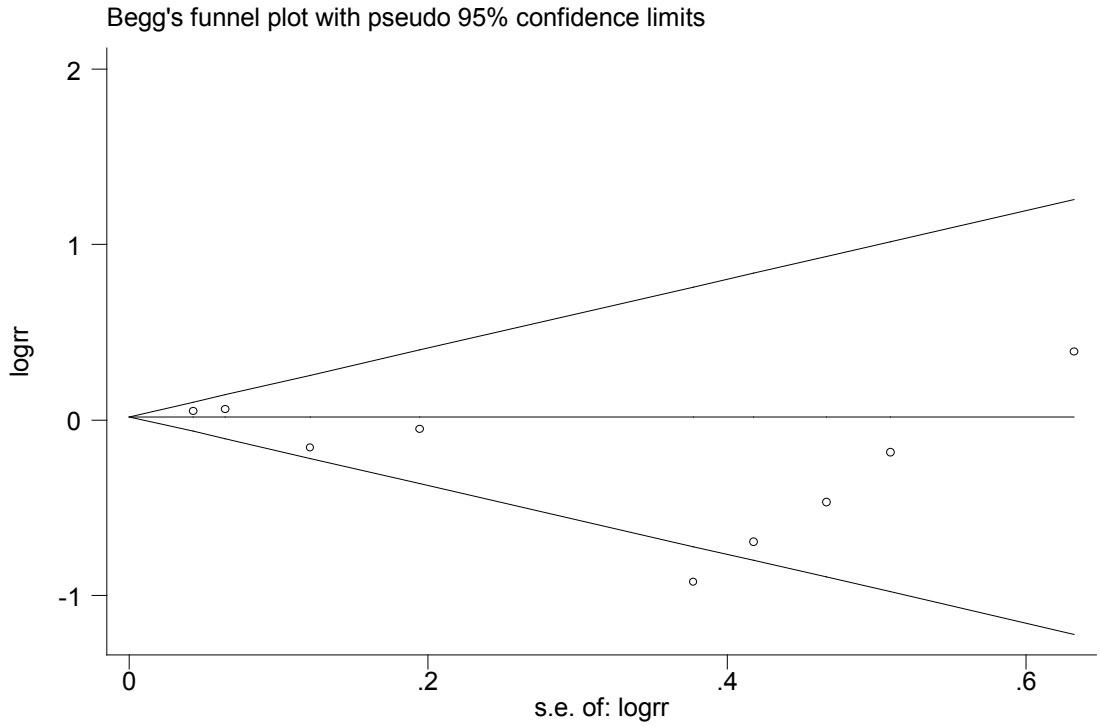
eFigure 7B. Funnel plot of the included studies: triple therapy vs ICS/LABA on the risk of death.



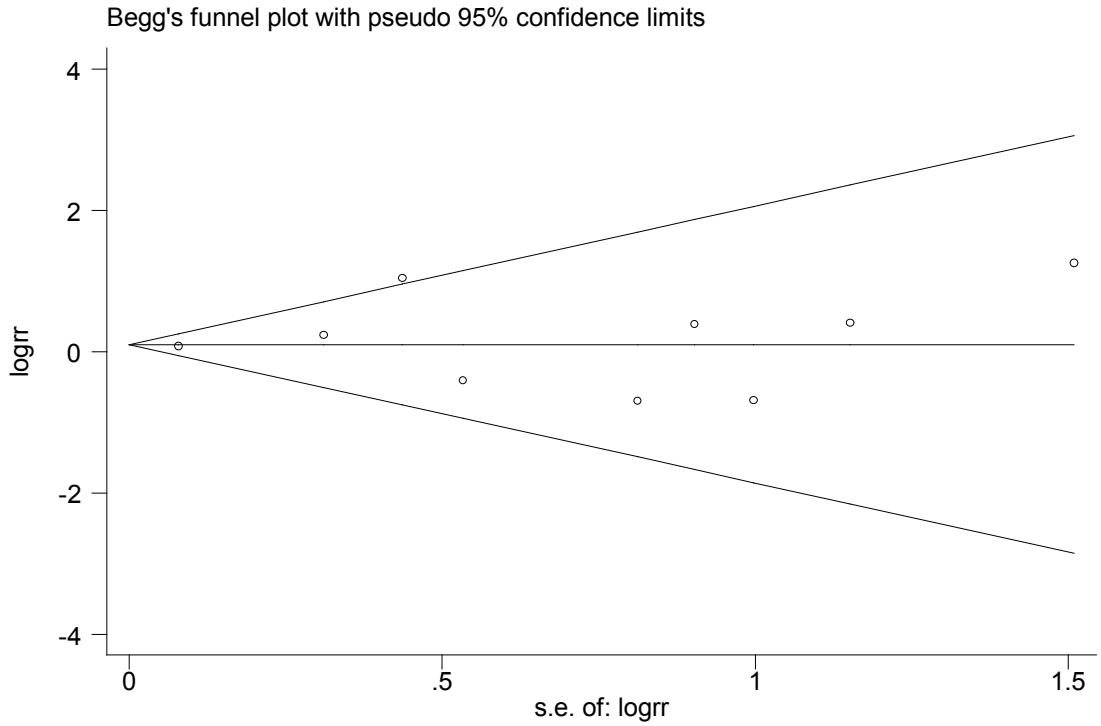
eFigure 7C. Funnel plot of the included studies: triple therapy vs ICS/LABA on the risk of AEs.



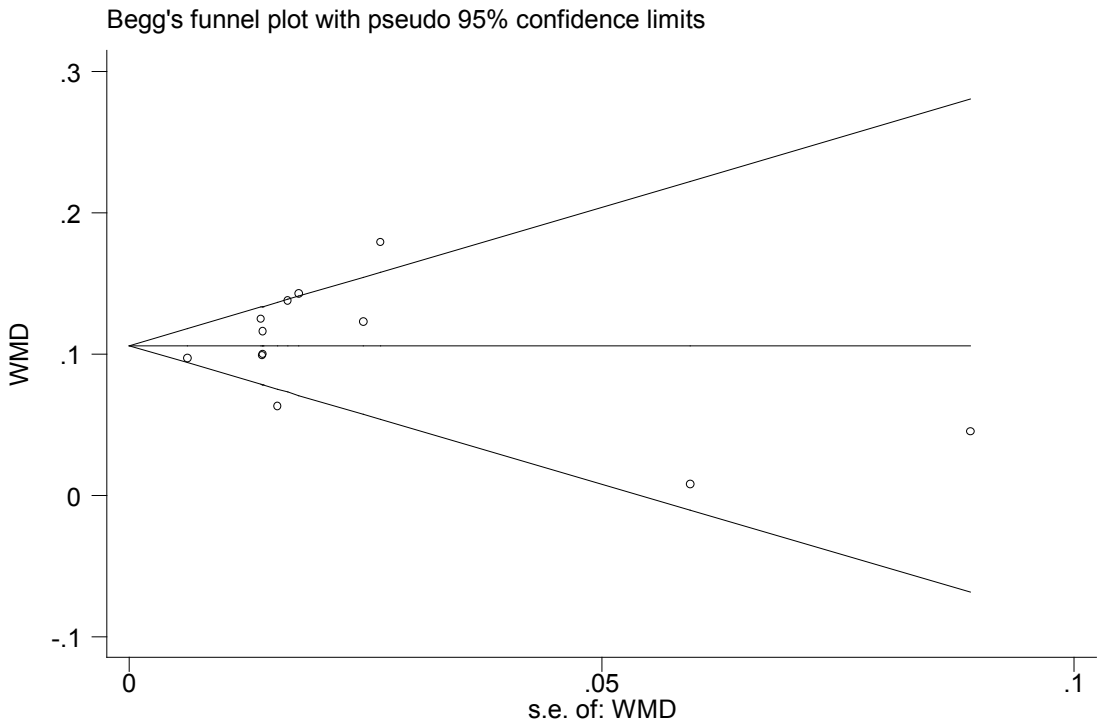
eFigure 7D. Funnel plot of the included studies: triple therapy vs ICS/LABA on the risk of SAEs.



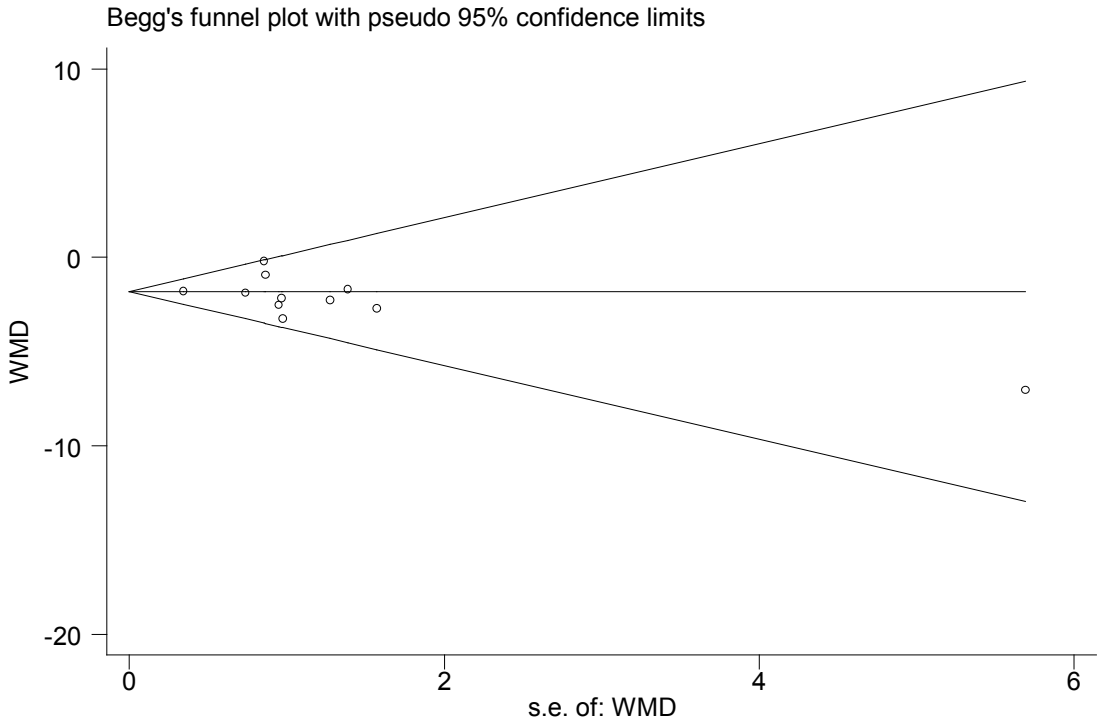
eFigure 7E. Funnel plot of the included studies: triple therapy vs ICS/LABA on the risk of pneumonia.



eFigure 7F. Funnel plot of the included studies: triple therapy vs ICS/LABA on the change of FEV1.



eFigure 7G. Funnel plot of the included studies: triple therapy vs ICS/LABA on the change of SERQ score.



eFigure 7H. Funnel plot of the included studies: triple therapy vs LAMA on the change of FEV1.