

# Efficacy of tiotropium in treating patients with moderate-to-severe asthma

## A meta-analysis and systematic review based on 14 randomized controlled trials

Jian-Feng Meng, MM\*, Hua Li, BM, Ming-Jie Luo, MM, Hai-Bin Li, MD

### Abstract

**Background:** The goal of the current meta-analysis and systematic review was to explore the efficacy of tiotropium in treating patients with moderate-to-severe asthma on the basis of qualified randomized controlled trials (RCTs).

**Methods:** The following online electronic databases, such as Cochrane, PubMed, and Embase database were screened to identify qualified studies updated to January 2019 through the use of index words. Several literatures that were relevant to the present analysis were also included. To further analyze the main outcomes, we utilized the odds ratios (OR), and mean difference (MD) along with its 95% confidence interval (95% CI).

**Results:** A total of 14 RCTs with 4998 patients in the tiotropium group and 5074 patients in the control group were included in the present study. On the basis of the pooled results, tiotropium was significantly associated with improved morning PEF (SMD: 3.29, 95%CI: 2.03–4.55), evening PEF (SMD: 3.36, 95%CI: 2.24–4.48), peak FEV (SMD: 2.67, 95%CI: 1.47–3.88), and trough FEV (SMD: 1.90, 95%CI: 0.87–2.92) vs the control group. Nevertheless, no significant difference was observed in peak FVC (SMD: 0.77, 95%CI: –0.21–1.76), trough FVC (SMD: 0.67, 95%CI: –0.18–1.53), AE (RR: 0.98, 95%CI: 0.94–1.02) and serious AE (RR: 1.08, 95%CI: 0.77–1.52) between the 2 groups.

**Conclusions:** In this review, we summarized the significant effect of tiotropium for the treatment of moderate-to-severe asthma, mainly in increasing morning PEF, evening PEF, peak FEV and trough FEV based on high-quality RCTs. Nevertheless, no significant difference in peak FVC, trough FVC, AE and serious AE was found between the 2 groups. A close comparison of the 2 groups revealed that more high-quality larger-sample RCTs are needed to gather more strong evidence on the therapeutic efficacy and safety of tiotropium for clinical practice.

**Abbreviations:** 95% CI 95% = confidence interval, AE = adverse event, FEV = forced expiratory volume, FVC = forced vital capacity, ICS = inhaled corticosteroids, LABA = inhaled long-acting beta 2 agonists, MD = mean difference, OR = odds ratios, PEF = peak expiratory flow, RCTs = randomized controlled trials, RR = relative risk.

**Keywords:** asthma, meta-analysis, randomized controlled trial, tiotropium

### 1. Introduction

Asthma is a type of respiratory disease that occurs due to chronic airway inflammation. It is generally characterized by infiltration

of eosinophils, activated mast cells and T lymphocytes into the bronchial wall. Cytokines released by TH2 cells and leukotrienes play a key role in mediating airway inflammation. Another feature of asthma is reversible ventilation dysfunction caused by excessive contraction of bronchial smooth muscle. Given the present understanding of the pathogenesis of asthma, clinical treatment mainly focuses on anti-inflammatory approaches and dilating the airway. According to the recommendation from the latest GINA Guidelines in 2015, anti-inflammatory drugs mainly include inhaled corticosteroids (ICS) and leukotriene antagonists, while bronchodilators mainly include inhaled long-acting beta 2 agonists (LABA).<sup>[1–4]</sup>

Tiotropium is a specific selective anticholinergic drug with a muscarinic receptor-like affinity and has been approved to treat chronic obstructive pulmonary disease. By binding to the muscarinic receptor on the bronchial smooth muscle, it can inhibit bronchoconstriction, bronchial vasodilation and mucus secretion caused by acetylcholine released from the parasympathetic nerve endings. Theoretically, tiotropium bromide is able to alleviate asthma symptoms, but debates exist concerning whether it can be used for routine treatment in clinical practice.<sup>[5–9]</sup> Hence, the current meta-analysis was conducted based on

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Department of Respiratory Medicine, Nanxishan Hospital of Guangxi Zhuang Autonomous Region, Gulin, Guangxi, China.

\* Correspondence: Jian-Feng Meng, Department of Respiratory Medicine, Nanxishan Hospital of Guangxi Zhuang Autonomous Region, No. 46 Chongxin Road, Xiangshan District, Gulin, Guangxi 541002, China (e-mail: mengjianfengm@sina.com).

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updated data and literature to gather available evidence to explore the clinical efficacy of tiotropium in treating patients suffering from moderate-to-severe asthma.

## 2. Methods

### 2.1. Ethics approval

The ethics approval was waived because the study does not involve any human participants and animals.

### 2.2. Search strategy

An electronic search of literature using Embase, Cochrane, and PubMed was conducted by 2 reviewers up to January 2019 in terms of the efficacy of tiotropium in treating patients with moderate-to-severe asthma. References from relevant studies and reviews were further searched to confirm retrieval of all possible pertinent trials. The following search terms were used: tiotropium, tiotropium bromide, asthma, cough variant asthma, wheezing, CVA, randomized, randomized controlled trial, and RCT. These terms were used in combination with “AND” or “OR”. The search process was carried out separately by 2 reviewers. Any differences were settled through the aid of a third party.

### 2.3. Selection criteria

To be included in the current meta-analysis, studies should meet the following criteria:

1. RCTs;
2. patients diagnosed with asthma as the research subjects;
3. the interventions of the experiment group were tiotropium; the interventions of the control groups were standard therapy or ICS or LABA;
4. only English publications were eligible.

Studies were excluded due to the following criteria:

1. duplicate publications, or shared contents and results;
2. data with obvious errors;

3. case report, case-control studies, conference report, theoretical research, meta-analysis, systematic review, economic analysis, expert comment, or real world study;
4. irrelevant outcomes.

The literature selection process was performed by 2 reviewers separately based on predefined criteria and any arising differences were settled by discussion with a third party.

### 2.4. Data extraction and quality assessment

We examined the data based on the included studies with 2 parts consisted, including the following 2 parameters:

1. basic information such as name of author, year of publication, interventions of the experiment group and the control group, sample size, gender, age, severity of asthma, and the Jadad score;
2. clinical outcomes including morning peak expiratory flow (PEF), evening PEF, peak forced expiratory volume (FEV), trough FEV, peak forced vital capacity (FVC), trough FVC, adverse event (AE), and serious AE as clinical outcomes.

To appraise the quality of the involved studies, we used the Jadad score checklist. In addition, all RCTs were under assessment from the 5 items: appropriateness of generation of randomized sequence, statement of randomization, detail of withdrawals and dropouts, use of double blinding, as well as the description of double blinding method. A score less than 3 in the included studies represented a low-quality and high bias risk, and a score greater than 3 represents a trial with high quality. The abovementioned process was separately conducted by 2 investigators; arising differences were settled by discussion to reach a consensus.

### 2.5. Statistics analysis

The meta-analysis was conducted through the use of the STATA 10.0 (TX). Heterogeneity of the trial results was assessed with the Chi-squared and  $I^2$  tests to select ideal analysis model (random-effects model or fixed-effects model);  $I^2 > 50\%$  and Chi-squared test  $P \leq .05$  reflected a high heterogeneity and the random-effects

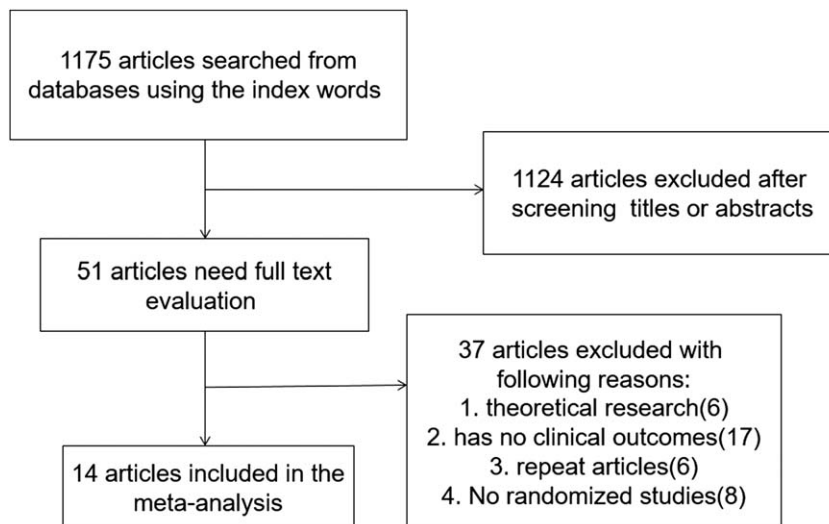


Figure 1. Flow diagram of the literature search and selection process.

**Table 1**  
The basic characteristics description of included studies.

Study	Treatment		No. of patients		Gender (M: male)	Age (mean±SD)	The severity of asthma	The Jadad score
	Tiotropium group	Control group	Tiotropium group	Control group				
Tom Fardon 2007	ICS+LABA+Tiotropium, 4 weeks	ICS+LABA, 4 weeks	25	25	11M	54±2.44	severe	4
Stephen P. Peters 2010	ICS+LABA+Tiotropium, 14 weeks	ICS, 14 weeks	203	196	69M	42.2±12.3	moderate	4
Eric D. Bateman 2011	ICS+Tiotropium, 16 weeks	ICS, 16 weeks	128	126	97M	43.3±12.3	moderate	6
Huib A. M. Kerstjens 2011	ICS+Tiotropium5 µg, 8 weeks	ICS, 8 weeks	104	103	46M	54.8±11.7	severe	4
Wolfgang Timmer 2015 a	ICS+LABA+once-daily Tiotropium5 µg, 4 weeks	ICS+LABA, 4 weeks	94	94	39M	44.3±13.2	moderate	4
Wolfgang Timmer 2015 b	ICS+LABA+twice daily Tiotropium2.5 µg, 4 weeks	ICS+LABA, 4 weeks	94	94	39M	44.3±13.2	moderate	4
Kai-Michael Beeh 2014 a	ICS+LABA+Tiotropium5 µg, 4 weeks	ICS+LABA, 4 weeks	146	144	67M	49.3±13.3	moderate	4
Kai-Michael Beeh 2014 b	ICS+LABA+Tiotropium2.5 µg, 4 weeks	ICS+LABA, 4 weeks	147	144	67M	49.3±13.3	moderate	4
Kai-Michael Beeh 2014 c	ICS+LABA+Tiotropium1.25 µg, 4 weeks	ICS+LABA, 4 weeks	146	144	67M	49.3±13.3	moderate	4
Huib A. M. Kerstjens 2015 a	ICS+LABA+Tiotropium5 µg, 24 weeks	ICS+LABA, 24 weeks	517	523	632M	43.1±12.9	moderate	6
Huib A. M. Kerstjens 2015 b	ICS+LABA+Tiotropium2.5 µg, 24 weeks	ICS+LABA, 24 weeks	519	523	632M	43.1±12.9	moderate	6
Elianne J L E Vrijlandt 2018 a	ICS+LABA+Tiotropium5 µg, 12 weeks	ICS+LABA, 12 weeks	31	34	61M	-	severe	6
Elianne J L E Vrijlandt 2018 b	ICS+LABA+Tiotropium2.5 µg, 12 weeks	ICS+LABA, 12 weeks	36	34	61M	-	severe	6
Huib A. M. Kerstjens 2012 a	ICS+LABA+Tiotropium, 48 weeks	ICS+LABA, 48 weeks	237	222	170M	53±12.4	severe	6
Huib A. M. Kerstjens 2012 b	ICS+LABA+Tiotropium, 48 weeks	ICS+LABA, 48 weeks	219	234	191M	53±12.4	severe	6
Stanley J. Szefler 2016 a	ICS+LABA+Tiotropium5 µg, 12 weeks	ICS+LABA, 12 weeks	130	134	183M	9.2±1.6	severe	6
Stanley J. Szefler 2016 b	ICS+LABA+Tiotropium2.5 µg, 12 weeks	ICS+LABA, 12 weeks	136	134	189M	8.8±1.7	severe	6
Eckard Hamelmann 2017 a	ICS+LABA+Tiotropium5 µg, 12 weeks	ICS+LABA, 12 weeks	130	135	162M	-	severe	6
Eckard Hamelmann 2017 b	ICS+LABA+Tiotropium2.5 µg, 12 weeks	ICS+LABA, 12 weeks	127	135	159M	-	severe	6
Eckard Hamelmann 2016 a	ICS+LABA+Tiotropium5 µg, 48 weeks	ICS+LABA, 48 weeks	134	138	177M	14.5±1.6	moderate	6
Eckard Hamelmann 2016 b	ICS+LABA+Tiotropium2.5 µg, 48 weeks	ICS+LABA, 48 weeks	125	138	169M	14.2±1.8	moderate	6
Pierluigi Paggiaro 2015 a	ICS+LABA+Tiotropium5 µg, 12 weeks	ICS+LABA, 12 weeks	155	155	111M	41.9±13	moderate	6
Pierluigi Paggiaro 2015 b	ICS+LABA+Tiotropium2.5 µg, 12 weeks	ICS+LABA, 12 weeks	154	155	124M	43.8±14	moderate	6
Christian Vogelberg 2015 a	ICS+LABA+Tiotropium5 µg, 12 weeks	ICS+LABA, 12 weeks	76	76	69M	8.8±1.7	moderate	6
Christian Vogelberg 2015 b	ICS+LABA+Tiotropium2.5 µg, 12 weeks	ICS+LABA, 12 weeks	74	76	69M	8.8±1.7	moderate	6
Christian Vogelberg 2015 c	ICS+LABA+Tiotropium1.25 µg, 12 weeks	ICS+LABA, 12 weeks	75	76	69M	8.8±1.7	moderate	6
Huib A M Kerstjens 2015 a	ICS+LABA+Tiotropium5 µg, 24 weeks	ICS+LABA, 24 weeks	517	541	446M	44.3±12.6	moderate	6
Huib A M Kerstjens 2015 b	ICS+LABA+Tiotropium2.5 µg, 24 weeks	ICS+LABA, 24 weeks	519	541	432M	43.4±12.9	moderate	6

\*ICS=inhaled corticosteroids, LABA=long-acting beta-agonist.

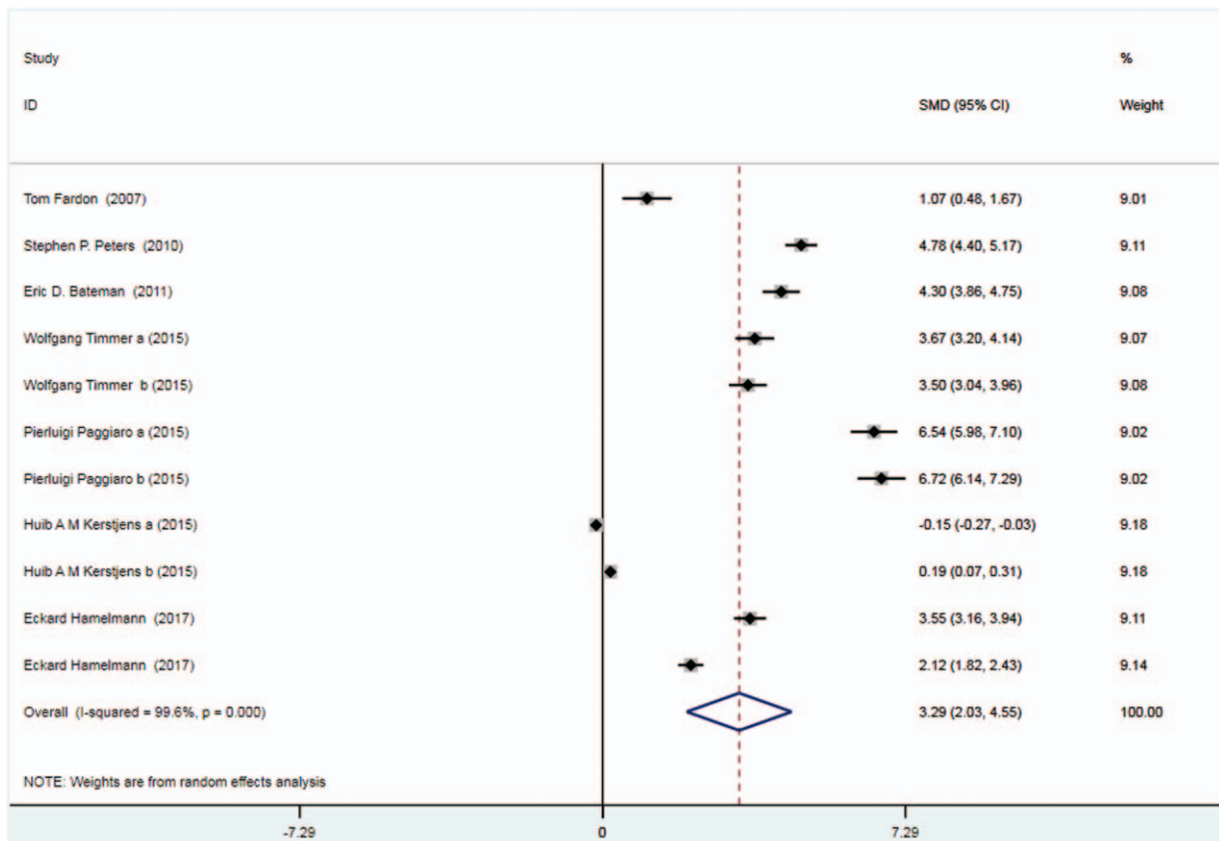


Figure 2. Forest plot for the result of morning PEF. PEF = peak expiratory flow.

model was utilized;  $I^2 \leq 50\%$  and Chi-squared test  $P > .05$  reflected an acceptable heterogeneity data with the assessment of the fixed-effects model. As for continuous variables, they were initially expressed as mean  $\pm$  standard deviation and then analyzed through the use of mean difference (MD). We presented categorical data by percentages and further analyzed it through odds ratio (OR) or relative risk (RR). RR along with 95% CI was used to analyze AE and serious AE. Morning PEF, evening PEF, peak FEV, trough FEV, peak FVC and trough FVC were analyzed by MD along with 95%CI.

**3. Results**

**3.1. Study characteristics**

Totally, 1175 publications were included based on the indexes. During initial screening of the abstracts and titles, 1124 publications were eliminated, leaving 51 publications for further assessment. During full-text screening and searching, 37 publications were excluded because of failure to meet the inclusion criteria: theoretical or economic research (6), lack of clinical outcomes (17), non-RCT (8), or duplicate articles (6). Therefore, a final total of 14 RCTs<sup>[8,10-22]</sup> were presented in the current meta-analysis, of which there were 4998 patients in the tiotropium group and 5074 patients in the control group (See Fig. 1). Table 1 shows the major characteristics of studies.

The basic information consisted of sample, gender, age, treatment, severity and the Jadad score. The main Jadad score of

the included studies was 5.43 which was greater than 3; thus, all the included studies were of high quality.

**3.2. PEF**

Seven trials with 2146 patients in the tiotropium group and 2197 patients in the control group studied morning PEF. On the basis of the  $I^2$  test-value ( $99.6\% > 50\%$ ) and Chi-squared test  $P$  value ( $.000 < .05$ ), the random effects model was selected for analysis of morning PEF. The pooled result showed that the tiotropium group was associated with significant effect in improving morning PEF vs the control group (SMD: 3.29, 95%CI: 2.03–4.55, Fig. 2).

Eight trials with 2412 patients in the tiotropium and 2465 patients in the control group reported evening PEF. On the basis of the  $I^2$  test-value ( $99.5\% > 50\%$ ) and Chi-squared test  $P$  value ( $.000 < .05$ ), the random effects model was applied to analyze evening PEF. Based on the pooled results, evening PEF was remarkably improved in the tiotropium group vs the control group (SMD: 3.36, 95%CI: 2.24–4.48, Fig. 3).

**3.3. FEV**

Six trials with 2162 patients in the tiotropium and 2227 patients in the control group reported peak FEV. On the basis of the  $I^2$  test value ( $99.6\% > 50\%$ ) and Chi-squared test  $P$  value ( $.000 < .05$ ), the random effects model was selected for analysis of peak FEV. The pooled result showed significantly improved trend of peak

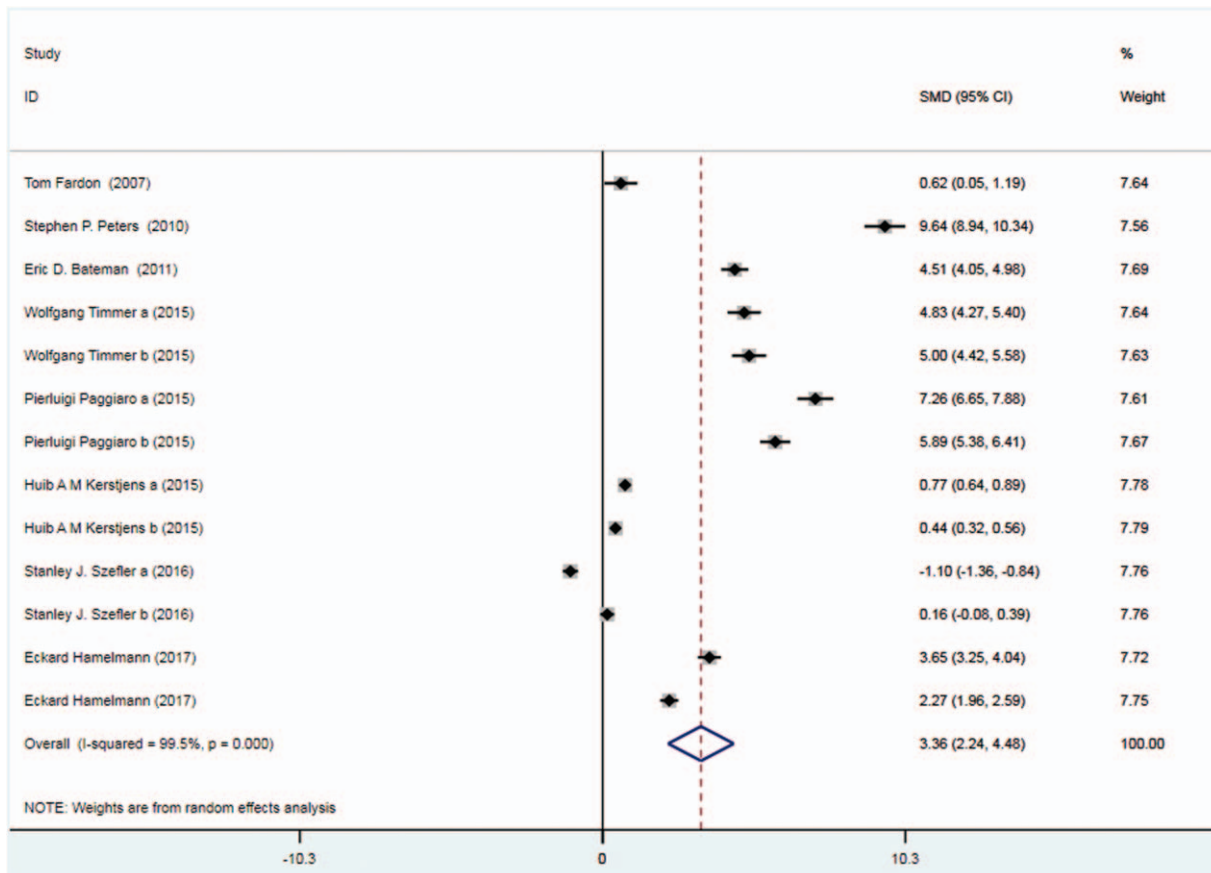


Figure 3. Forest plot for the result of evening PEF. PEF = peak expiratory flow.

FEV in the tiotropium group vs the control group (SMD: 2.67, 95%CI: 1.47–3.88, Fig. 4).

Five trials with 1896 patients in the tiotropium and 1959 patients in the control group reported the trough FEV. On the basis of the  $I^2$  test value (99.3% > 50%) and Chi-squared test  $P$  value (.000 < .05), the random effects model was selected for analysis of trough FEV. According to the pooled results, there was remarkable improvement of trough FEV in the tiotropium group vs the control group (SMD: 1.90, 95%CI: 0.87–2.92, Fig. 5).

**3.4. FVC**

Four trials with 1818 patients in the tiotropium and 1896 patients in the control group reported peak FVC. On the basis of the  $I^2$  test value (99.4% > 50%) and Chi-squared test  $P$  value (.000 < .05), the random effects model was selected for analysis of peak FVC. Based on the pooled results, no significant difference in peak FVC was found between the 2 groups (SMD: 0.77, 95% CI: -0.21–1.76, Fig. 6).

Four trials with 1818 patients in the tiotropium and 1896 patients in the control group showed the results of trough FVC. On the basis of the  $I^2$  test value (99.1% > 50%) and Chi-squared test  $P$  value (.000 < .05), the fixed effects model was selected for analysis of trough FVC. Based on the pooled result, no significant difference in trough FVC was identified between the two groups (SMD: 0.67, 95%CI: -0.18–1.53, Fig. 7).

**3.5. AE**

Thirteen trials with 4973 patients in the tiotropium and 5049 patients in the control group reported AE. On the basis of the  $I^2$  test value (0.0% < 50%) and Chi-squared test  $P$  value (.817 > .05), the fixed effects model was selected for analysis of AE. According to the pooled result, no significant difference in the incidence of AE was observed between the 2 groups (RR: 0.98, 95%CI: 0.94–1.02, Fig. 8).

Nine trials with 2212 patients in the tiotropium and 2234 patients in the control group reported serious AE. On the basis of the  $I^2$  test value (0.0% < 50%) and Chi-squared test  $P$  value (.967 > .05), the fixed effects model was selected for analysis of serious AE. Based on the pooled result, no significant difference in the incidence of serious AE was found between the two groups (RR: 1.08, 95%CI: 0.77–1.52, Fig. 9).

**3.6. Quality assessment and potential bias**

According to the predefined criteria, a total of 20 publications were included for analysis in the present meta-analysis. We performed quality assessment for potential bias through the use of funnel plot, Begg and Mazumdar rank test, and Egger test. Notable symmetry was found through the funnel plot for log RR in serious AE of the included studies, indicating no remarkable publication bias (Fig. 10). In addition, we identified significant symmetry by the use of Begg and Mazumdar rank test ( $Z = -2.85, P = .009$ ). Nonetheless, no significant publication bias was observed according to the Egger test results ( $P = .009$ ).

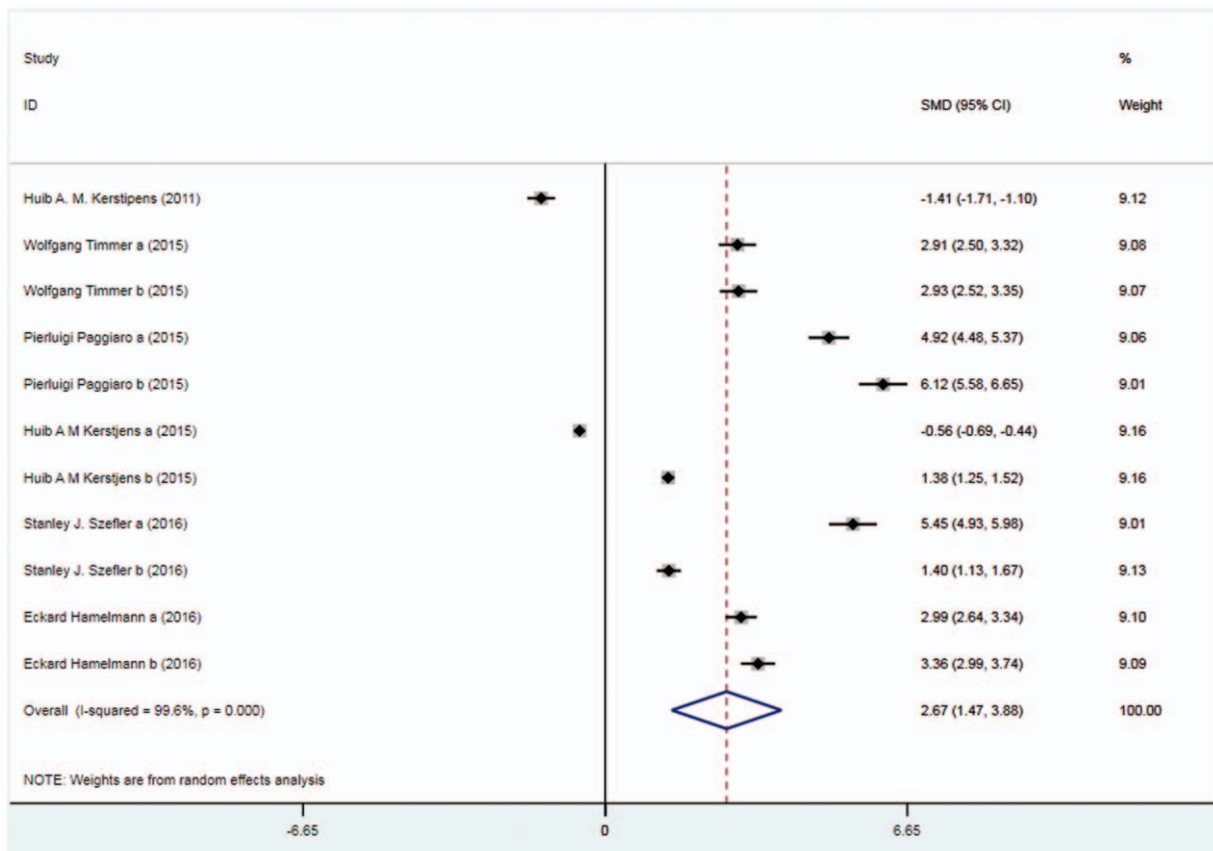


Figure 4. Forest plot for the result of peak FEV. FEV = forced expiratory volume.



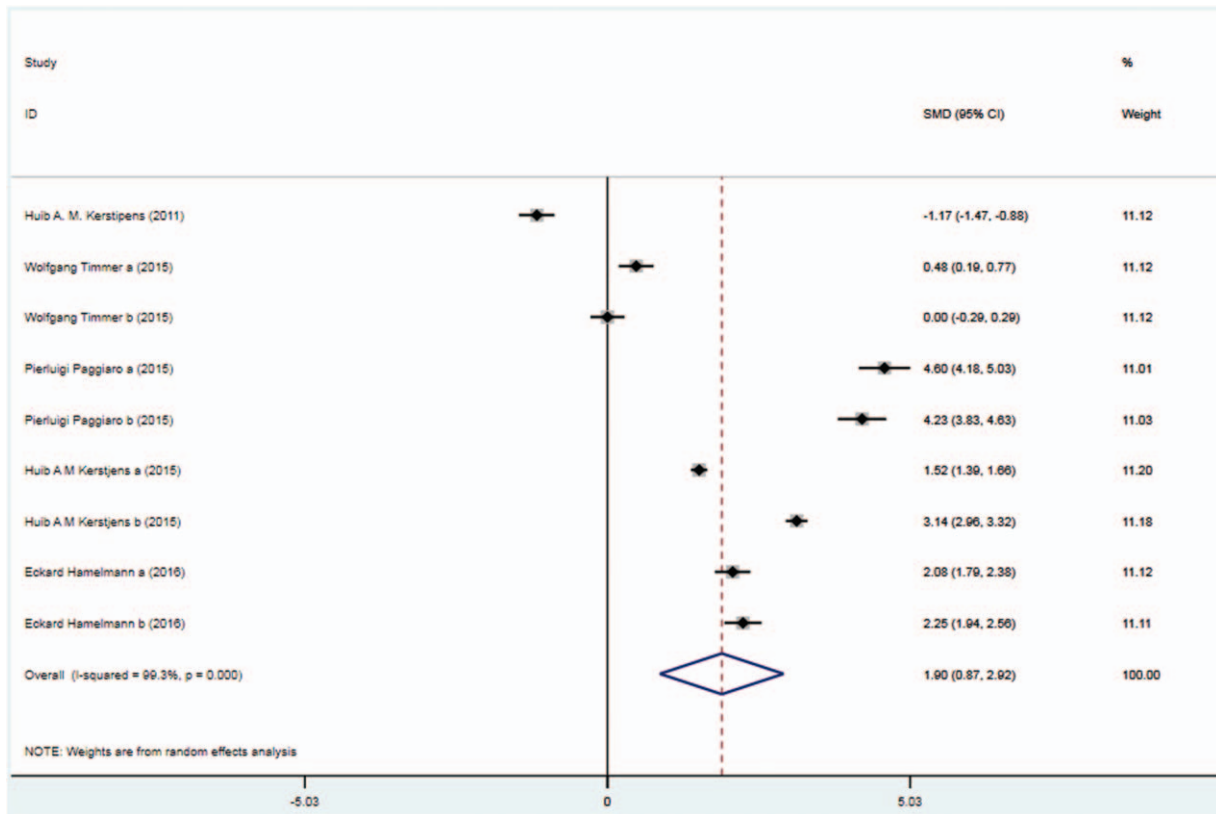


Figure 5. Forest plot for the result of trough FEV. FEV = forced expiratory volume.

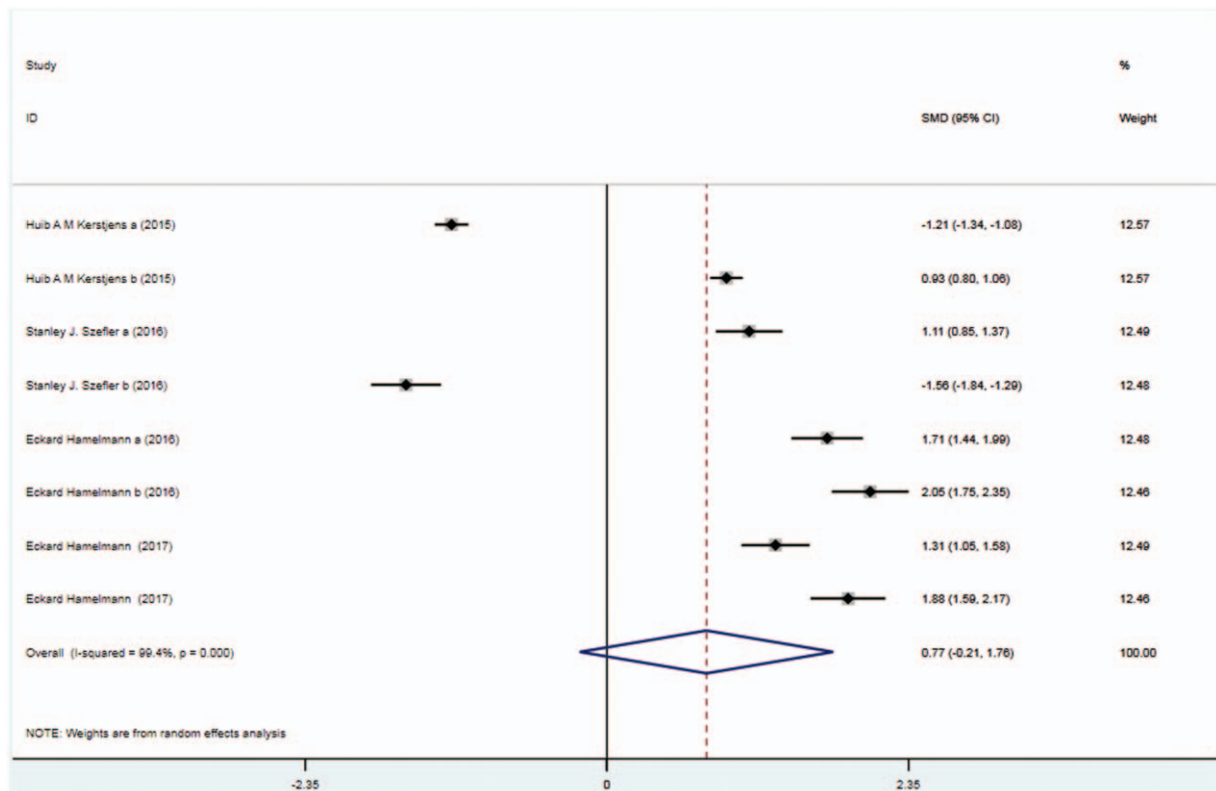


Figure 6. Forest plot for the result of peak FVC. FVC = forced vital capacity.

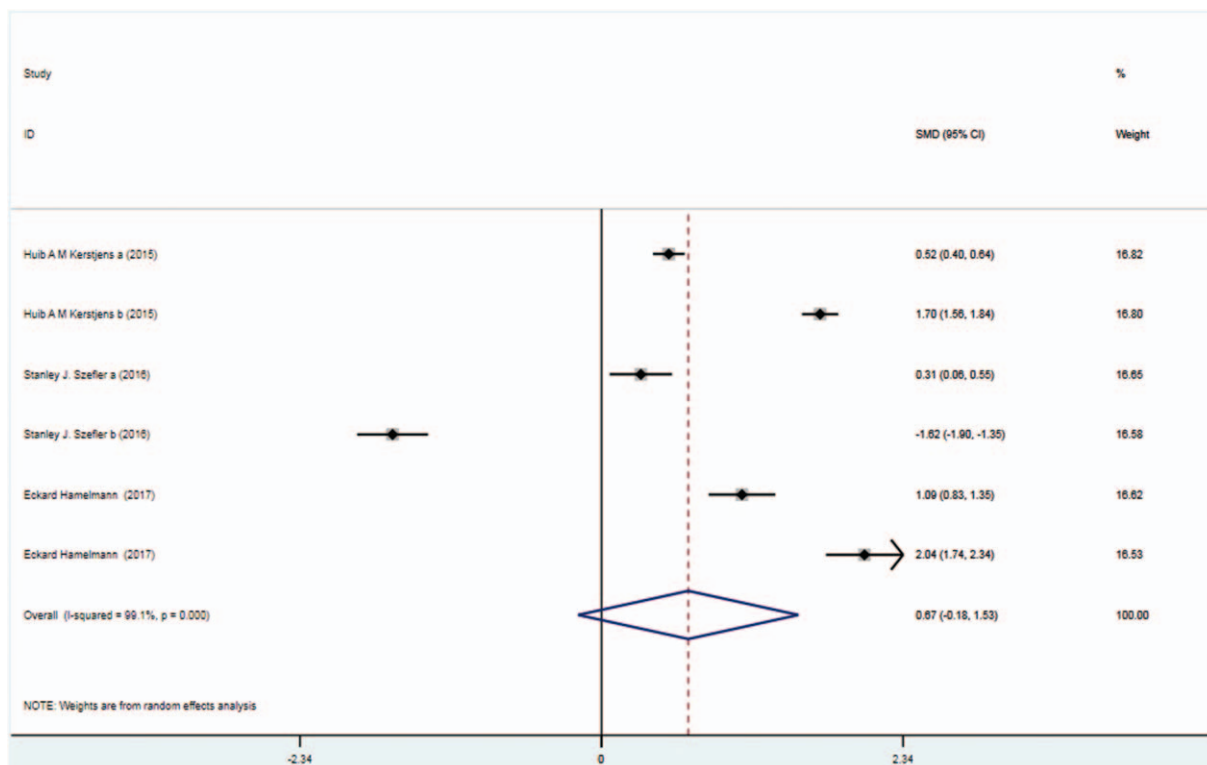


Figure 7. Forest plot for the result of trough FVC. FVC = forced vital capacity.

#### 4. Discussion

On the basis of earlier studies supported by Rodrigo et al,<sup>[23]</sup> 3 studies identified the remarkable effect of tiotropium in improving asthma by 100 mL ( $P < .001$ ) and FEV1 peak (mean change from baseline) by 120 mL ( $P < .001$ ) vs the placebo. The percentage of patients was decreased significantly by tiotropium who were suffering from an Asthma Control Questionnaire 7 worsening episode (a change from trial baseline of 0.5 points or more) vs the placebo (2.1% vs 4.8%, number needed to treat 1/4 38). Tiotropium also significantly reduced the number of patients with one or more exacerbation vs the placebo (17.6 vs 23.8%, number needed to treat 1/4 16). Nevertheless, there were no significant differences between the 2 groups in AEs (27.3% vs 27.1%), serious AEs (6.5% vs 7.1%), rescue medication use, withdrawals, and withdrawals due to AEs. Tiotropium 2.5 mg and 5.0 mg once daily contributed to the equivalent effects. Ian et al<sup>[24]</sup> concluded that, compared with the placebo, the additional use of tiotropium was associated with significant improvement in all spirometric indices, including trough and peak FEV1 (WMD 0.13 L, 95% CI 0.09–0.18 L,  $P < .001$ ; and WMD 0.10 L, 95% CI 0.06–0.14 L,  $P < .001$ , respectively), morning and evening PEF (WMD 20.59 L/min, 95% CI 15.36–25.81 L/min,  $P < .001$ ; and WMD 24.95 L/min, 95% CI 19.22–30.69 L/min,  $P < .001$ , respectively), the area under the curve of the first 3 hours of FVC (WMD 0.11 L, 95% CI 0.06–0.15 L,  $P < .001$ ), trough and peak FVC (WMD 0.1 L, 95% CI 0.05–0.15 L,  $P < .001$ ; and WMD 0.08 L, 95% CI 0.04–0.13 L,  $P < .001$ ,

respectively), and the area under the curve of the first 3 hours of FEV1 (WMD 0.13 L, 95% CI 0.08–0.18 L,  $P < .001$ ). The mean change in the 7-point Asthma Control Questionnaire score (WMD 0.12, 95% CI 0.21–0.03,  $P < .01$ ) was markedly lower in tiotropium group, but it was not clinically important. There were no significant differences in Asthma Quality of Life Questionnaire score (WMD 0.09, 95% CI 0.01–0.20,  $P < .09$ ), night awakenings (WMD 0.00, 95% CI 0.05–0.05,  $P < .99$ ) or rescue medication use (WMD 0.18, 95% CI 0.36–0.00,  $P < .06$ ). We noticed no significant increase in AEs based on the results of the tiotropium group (OR 0.80, 95% CI 0.62–1.03,  $P < .08$ ).

Asthma is known as a common clinical airway obstructive disease and bronchodilators are commonly used for controlling asthma symptoms. The ultimate goal of asthma management is to not only control asthma symptoms but also to reduce the incidence of acute attacks and AEs. The pathogenesis of asthma explains why inhalation of ICS and short-acting  $\beta$ -2 receptor antagonist (SABA) are recommended for the treatment of persistent asthma. ICS controls airway inflammation and SABA relieves airway spasm to control acute asthma symptoms. To reduce the side effects of the drug, the guidelines state that the more asthma is treated, the higher the dose of inhaled ICS should be taken. Despite with the largest doses of inhaled ICS, some asthma still cannot be controlled. Therefore, new valid and alternative drugs are in great demand to treat asthma in clinical practice. Tiotropium bromide is a highly selective receptor antagonist for the muscarinic acetylcholine (Ach) receptor, and it

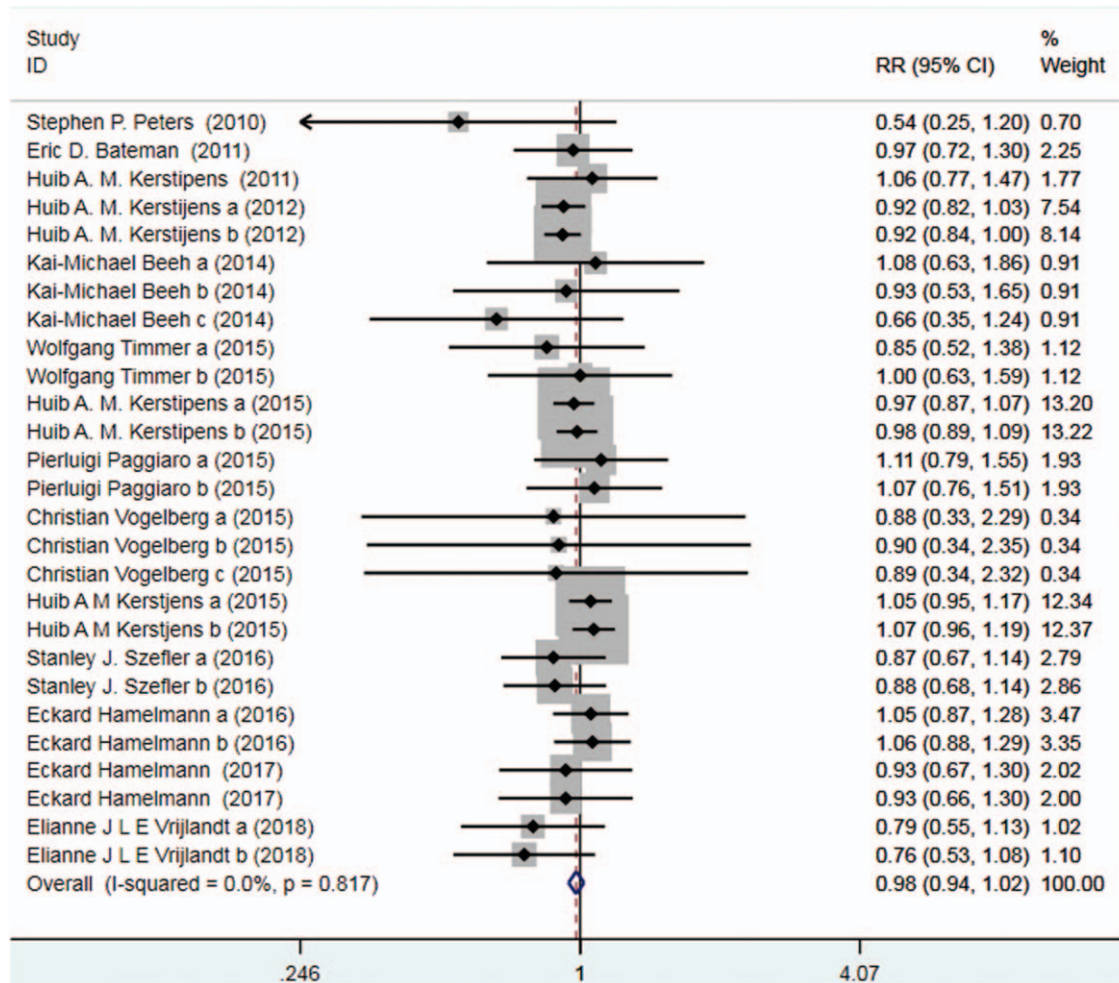


Figure 8. Forest plot for the result of AE. AE = adverse event.

has the effect of continuous airway dilation for 16 hours due to slow dissociation from the Ach M3 receptor.

The current meta-analysis extends efforts with an attempt to confirm the efficacy of tiotropium for asthma. We conclude the following advantages of the current study: the findings obtained from the current systemic review might be more convincing than any individual study among all included studies because the efficacy of tiotropium in treating patients suffering from moderate-to-severe asthma was quantitatively determined using pooled large sample size; the strict inclusion and exclusion criterion were used to select qualified studies; all the data were analyzed by standard statistical analysis to make sure that the results were accurate. All the included studies were high-quality RCTs, making the conclusion clinically significant.

Admittedly, several limitations of the present analysis should be acknowledged. It was possible to include the following factors:

1. only RCTs were included;
2. the predefined criteria were different for patients among various studies;
3. types of drug and dosage were various;
4. different severities of asthma;

5. we used  $I^2$  to assess the heterogeneity of the included studies and decided to select which kind of model (the random effects model or fixed effects model). If  $I^2 > 50\%$ , meaning that there was a high heterogeneity, and the index was analyzed by the random effects model. If  $I^2 < 50\%$ , meaning that there was a low heterogeneity, and the index was analyzed by the fixed effects model. Morning PEF, evening PEF, peak FEV, trough FEV, and peak FVC were analyzed by the random effects model. So the included studies on morning PEF, evening PEF, peak FEV, trough FEV, and peak FVC has high heterogeneity;
6. we used the pooled data for analysis; data of individual patients were unavailable, which limit more comprehensive analyses.

Considering the limitation of number among included studies based on earlier meta-analyses, we conduct a new and more comprehensive meta-analysis to further explore the accurate efficacy of tiotropium in treating moderate-to-severe asthma. Based on the available evidence, tiotropium could increase morning PEF, evening PEF, peak FEV and trough FEV vs the control group based on high-quality RCTs. Besides, there was no significant difference in peak FVC, trough FVC, AE and serious



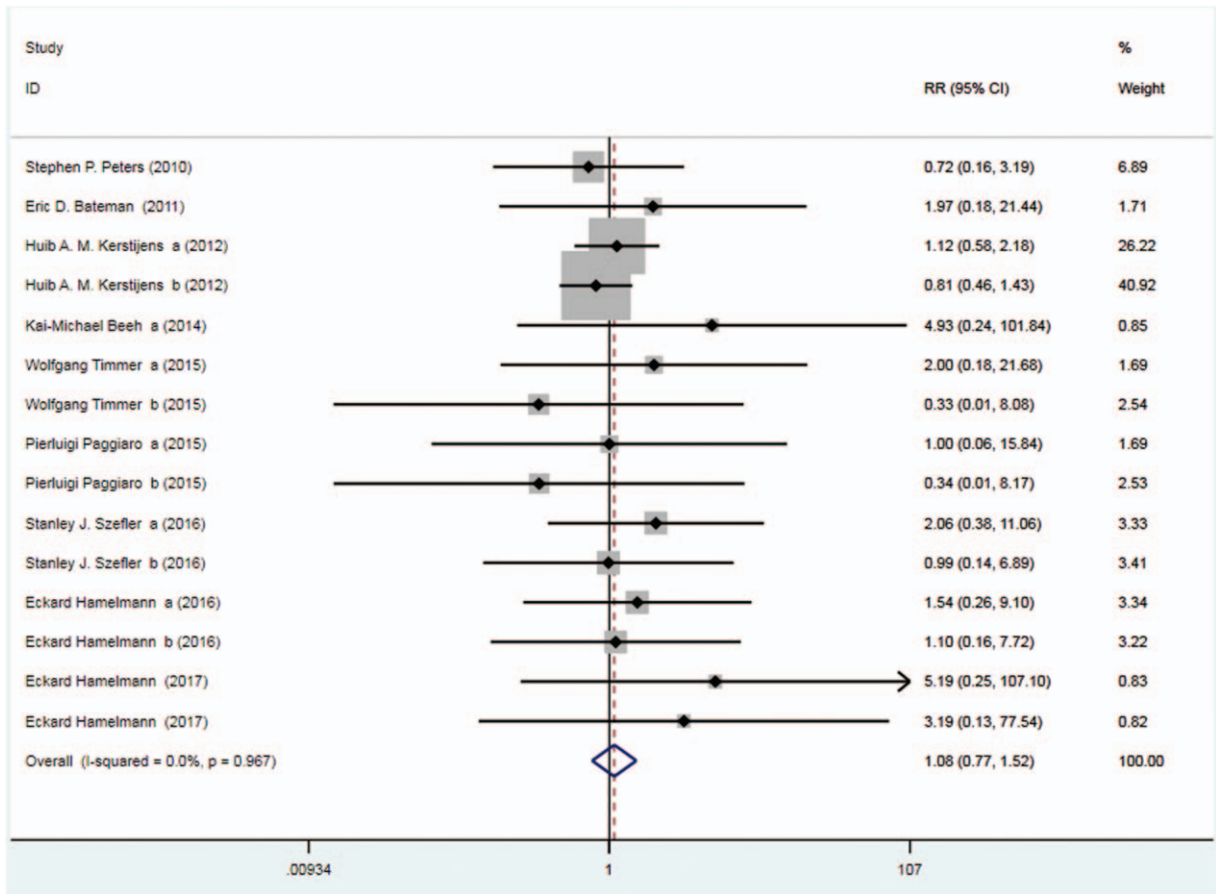


Figure 9. Forest plot for the result of serious AE. AE = adverse event.

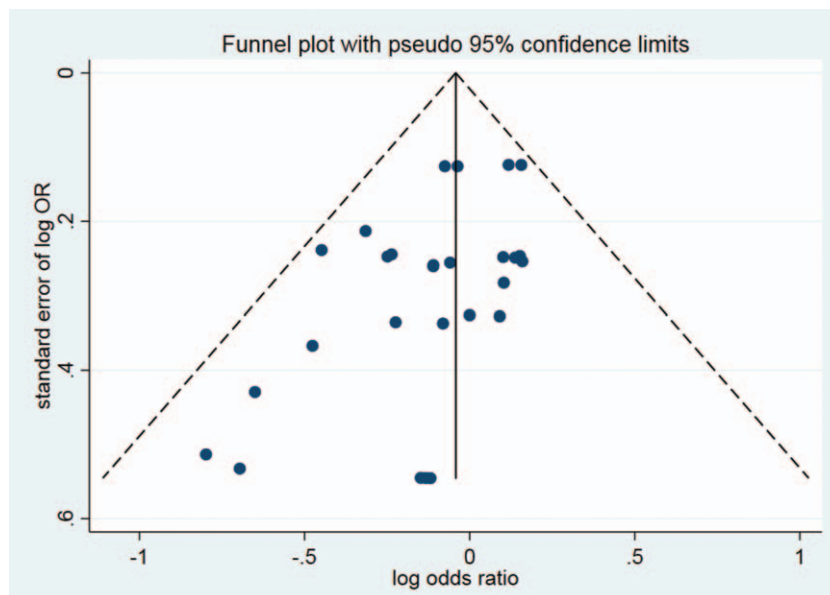


Figure 10. Funnel plot of studies included in the meta-analysis.

AE between the 2 groups. Given that there was no significant publication bias and the main Jadad score of included studies was 5.43, high quality of all the included studies should be confirmed. Furthermore high-quality, larger-sample RCTs are warranted to gather more solid evidence of the safety profile of tiotropium in clinical practice.

### Author contributions

**Formal analysis:** Hua Li, Hai-Bin Li.

**Investigation:** Hua Li.

**Methodology:** Ming-Jie Luo.

**Resources:** Ming-Jie Luo.

**Supervision:** Jian-Feng Meng.

**Validation:** Ming-Jie Luo.

**Writing – original draft:** Jian-Feng Meng.

**Writing – review & editing:** Hai-Bin Li.

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