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Efficacy and safety of dupilumab for the treatment of uncontrolled asthma: a meta-analysis of randomized clinical trials

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Abstract

Background: Several recent clinical trials have assessed the effects of dupilumab in uncontrolled asthma, but reached no definite conclusion. We therefore conducted this meta-analysis to evaluate the overall efficacy and safety of dupilumab for the treatment of uncontrolled asthma.

Methods: All randomized controlled trials were included. Standard mean differences (SMD) or relative risks (RR) were calculated using Fixed-or random-effects models.

Results: Five studies involving 3369 patients were identified. Pooled analysis showed significant improvements in the first-second forced expiratory volume (FEV_1) (SMD = 4.29, 95% CI: 2.78–5.81) and Asthma Quality of Life Questionnaire scores (SMD = 4.39, 95% CI: 1.44–7.34). Dupilumab treatments were also associated with significantly decreased 5-item Asthma Control Questionnaire scores (SMD = − 4.95, 95% CI: − 7.30 to 2.60), AM and PM asthma symptom scores (SMD = − 5.09, 95% CI: − 6.40 to − 3.77; SMD = − 4.92, 95% CI: − 5.98 to − 3.86, respectively), and severe exacerbation risk (RR = 0.73; 95% CI: 0.67–0.79) compared with placebo, with similar incidence of adverse events (RR = 1.0; 95% CI: 0.96–1.04).

Conclusion: Dupilumab treatment is relatively well-tolerated and could significantly improve FEV_1, symptoms, asthma control, and quality of life, and reduced severe exacerbation risk in patients with uncontrolled asthma.

Keywords: Dupilumab, Meta-analysis, Randomized control trial, Uncontrolled asthma

Introduction

Asthma is one of the most common chronic diseases and affects around 334 million people worldwide [1], of whom approximately 20–25% have uncontrolled disease [2]. Many of these patients have substantially reduced lung function and a higher risk of disease exacerbation, despite maximum treatment, and require the use of a considerable proportion of health care resources [3, 4]. Immunologically, type 2 cytokines (specifically interleukin [IL]-4, IL-5, and IL-13) are recognized as playing a substantial pathobiological role in asthma [5–7]. These cytokines link to a type-2/T-helper-2-cell (Th2)-high molecular asthma phenotype in up to 50% of asthmatic patients, across all levels of severity [8–10].

Dupilumab, a fully human monoclonal antibody, is directed against the alpha subunit of the IL-4 receptor, thereby blocking both IL-4 and IL-13 signaling, and hence type 2 inflammation [11]. It has been approved for the treatment of moderate-to-severe atopic dermatitis [12]. Several randomized, placebo-controlled studies (RCTs) have shown efficacy of dupilumab in patients with uncontrolled asthma. However, because the sample sizes of these studies were varied and results were less consistent, the evidence is insufficient for drawing robust conclusions. Therefore, we conducted a meta-analysis to assess the overall efficacy and safety of dupilumab treatment for uncontrolled asthma.

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Fig. 1 Flow chart of study identification, inclusion, and exclusion
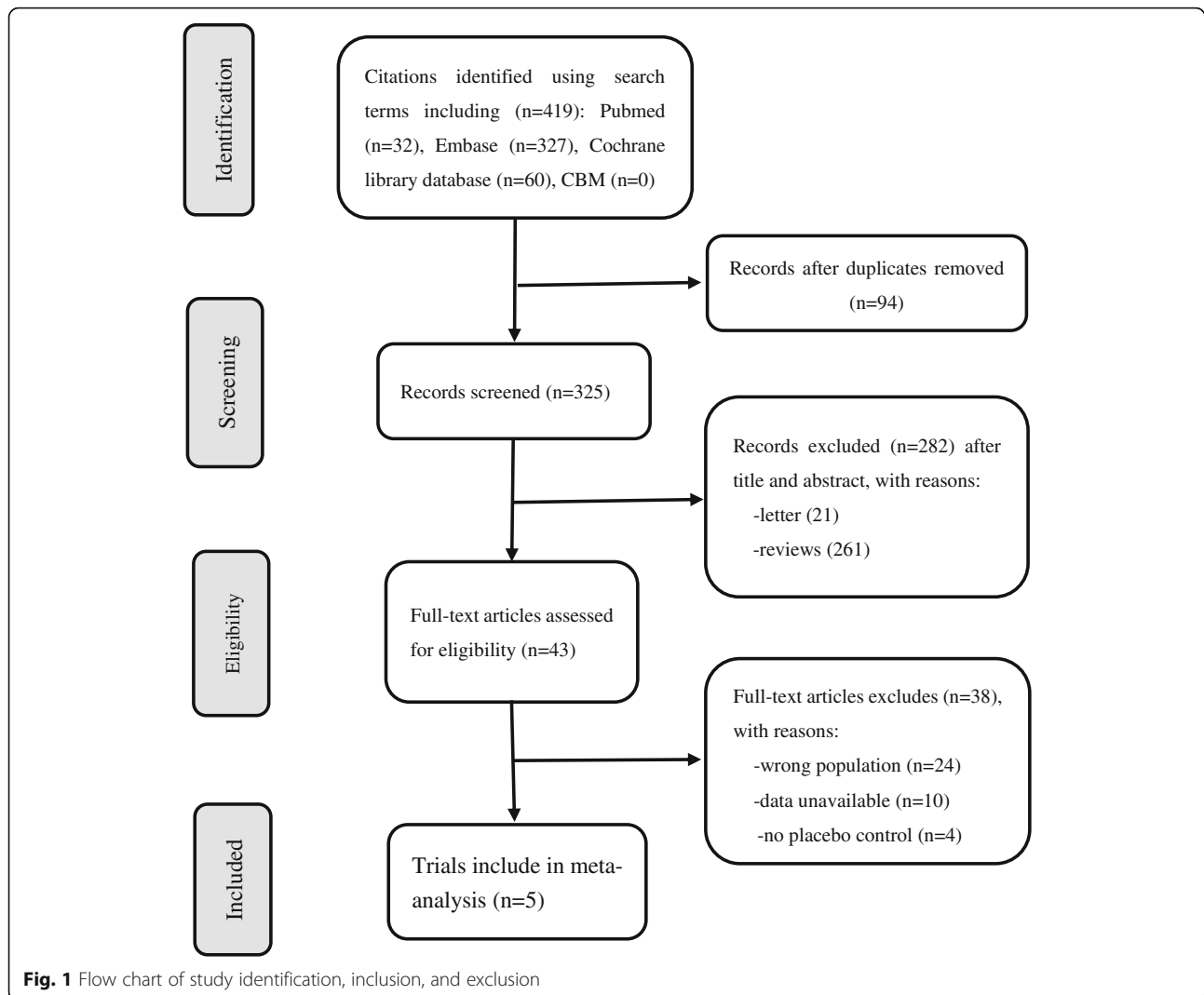
Methods

Data sources and searches

We searched PubMed, Embase, the Cochrane Library and Chinese Biological Medicine (CBM) databases for articles published up to June 30, 2018, to identify all trials assessing dupilumab therapy for patients with uncontrolled asthma, using the search terms: "asthma" and "dupilumab". Publication species was limited to humans. In addition, relevant review articles and their reference lists were checked manually.

Study selection

Studies were considered eligible if they met the following criteria: 1) trials recruited adults/adolescents (≥ 12 years old) diagnosed with uncontrolled asthma, 2) participants received dupilumab therapy at any dose, 3) RCTs, and 4) RCTs reporting the following outcomes: lung function (FEV_1), he 5-item Asthma

Control Questionnaire (ACQ-5) score, fractional exhaled nitric oxide (FE_{NO}), AM and PM asthma symptom scores, quality of life (AQLQ), severe exacerbation rate, or adverse events. Two investigators (XFX and MZ) independently screened all references according to the selection criteria. Disagreements were resolved through discussion.

The patients were diagnosed with asthma persisting for 1 year or more, according to the Global Initiative for Asthma 2009 or 2014 guidelines [13, 14]. Uncontrolled asthma was defined based on current treatment with a medium-to-high-dose inhaled glucocorticoid (fluticasone propionate at a total daily dose of ≥500 μg or equipotent equivalent), plus up to 2 additional controllers (e.g., a long-acting β2-agonist or leukotriene receptor antagonist); a forced expiratory volume in 1 s (FEV_1) ≤ 80% of the predicted normal value before bronchodilator use (or ≤ 90% of the

Table 1 Characteristic of randomized controlled trials included

Reference	phase	Country	Asthma severity	Patients(n) dupilumab/placebo	Treatment duration	Follow up	Dosage	Outcomes
Wenzel 2013 [27]	2A	The US	Moderate-to-severe; blood eosinophil count of at least 300 cells/μl	52/52	12 weeks	8 weeks	300 mg q1w	FEV_1; PEF; ACQ5 score; FE_{NO}; Asthma exacerbations; Morning and evening asthma score
Wenzel 2016 [15]	2b	Multinational	Uncontrolled moderate-to-severe asthma	611/158	24 weeks	12 weeks	200 mg q4w 300 mg q4w 200 mg q2w 300 mg q2w	FEV_1; ACQ5 score; FE_{NO}; AQLQ; Severe asthma exacerbations; Morning and evening asthma score
Castro 2018 [26]	3	Multinational	Uncontrolled moderate-to-severe asthma	Group 1: 631/313 Group 2: 632/321	52 weeks	12 weeks	200 mg q2w 300 mg q2w	FEV_1; PEF; ACQ5 score; FE_{NO}; AQLQ; Severe asthma exacerba-tions; Morning and evening asthma score
Rabe 2018 [25]	3	Multinational	Oral glucocorticoid–dependent severe asthma	103/107	24 weeks	NM	300 mg q2w	FEV_1; FE_{NO}; Severe asthma exacerbations Reduction in the oral glucocorticoid dose
Weinstein 2018 [24]	2b	Multinational	Uncontrolled persistent asthma	Group 1: 92/56 Group 2: 157/84	24 weeks	NM	200 mg q2w 300 mg q2w	FEV_1; Severe asthma exacerbations

Abbreviations: FEV_1 forced expiratory volume in 1 s, PEF peak expiratory flow, ACQ-5 5-item Asthma Control Questionnaire, FE_{NO} fractional exhaled nitric oxide, AQLQ the Asthma Quality of Life Questionnaire, NM not mentioned, q1w once weekly, q2w every 2 weeks, q4w every 4 weeks

predicted normal value in those 12–17 years of age); FEV_1 reversibility of at least 12% and 200 ml [15]; the 5-item Asthma Control Questionnaire (ACQ-5) score ≥ 1.5 (on a scale from 0 [no impairment] to 6 [maximum impairment]; the minimal clinically important difference is 0.5) [16]; and a worsening of asthma in the previous year that led to hospitalization, emergency medical care, or treatment with systemic glucocorticoids ≥3 days [15]. Asthma symptom scores are patient-reported measures of asthma symptoms, taken upon waking and in the evening. Their effects on activities (PM) and sleep (AM) were noted. These symptom scores range from 0 to 4, with higher scores indicating greater disruption [15]. A severe exacerbation was defined as a deterioration of asthma that required the use of systemic corticosteroids for at least 3 days, or hospital admission, or an emergency department visit because of asthma, treated with systemic corticosteroids [17]. The AQLQ is a patient-reported measure of the effect of asthma on quality of life; higher scores indicate a better quality of life; a global score is calculated and ranges from 0 to 7 [15].
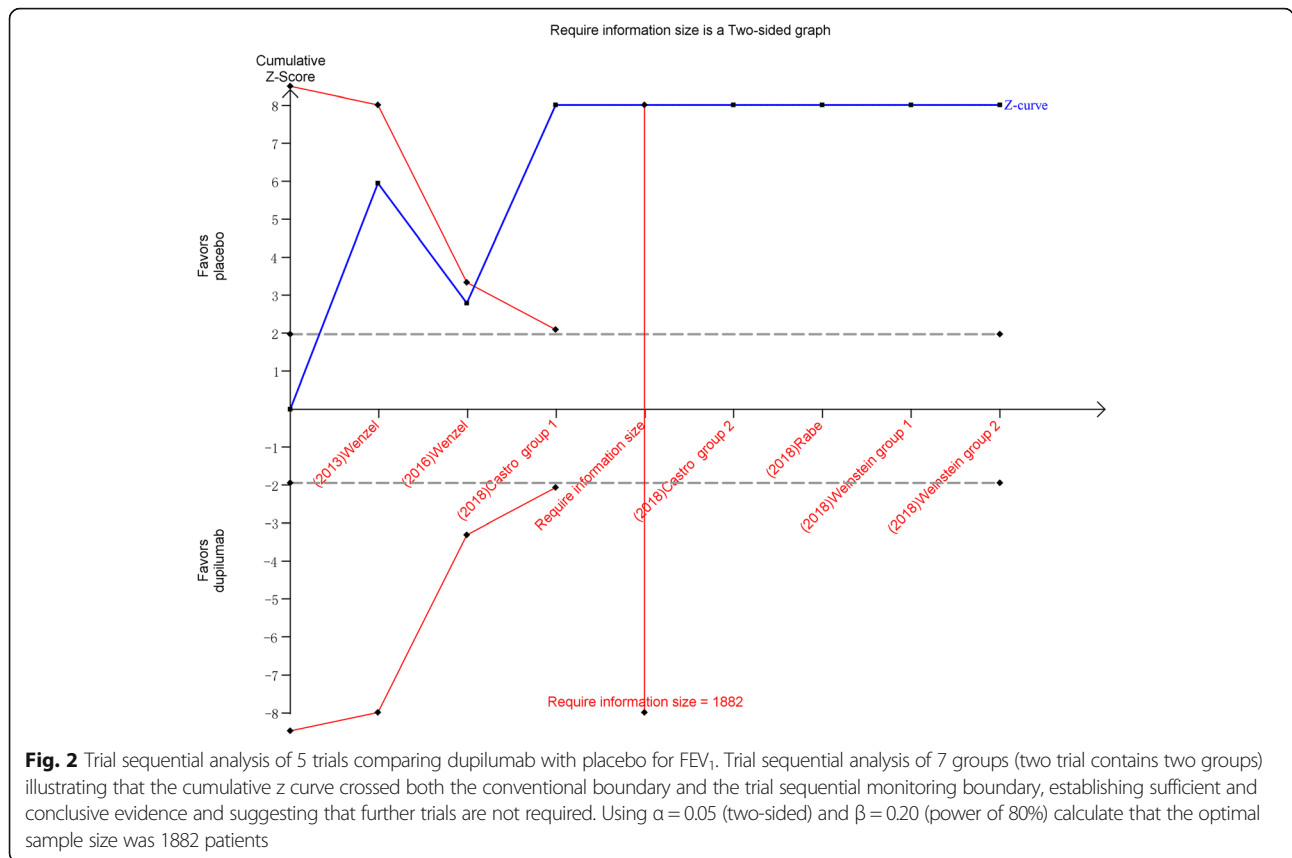
Data extraction and quality assessment
The Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) statement was followed. Two authors (XFX and MZ) performed data extracted and recorded desirable information of each enrolled study in a standard form as recommended by Cochrane [18]. Any disagreement was resolved through discussion or adjudicated by a third author (HXW). In addition, we evaluated the risk of bias using the Cochrane Collaboration's domains [19].

Statistical analyses
Intervention effects were presented using risk ratios (RR) and 95% confidence intervals (CIs) for dichotomous data and using mean differences (MD) and 95% CIs for continuous data. If a trial presented more than 2 intervention groups, we combined 2 or 3 groups into a single group according to the Cochrane handbook [19]. Heterogeneity was quantified by I^2 statistic and the χ^2 test. Random-effects model was performed in the presence of high heterogeneity ($I^2 > 50\%$); otherwise, fixed-effects model was applied [20]. Meta-regression was used to explore potential sources of heterogeneity. Funnel plots with the Begg's and Egger's tests were used to test publication bias [21]. All statistical analysis was accomplished by an independent statistician using Review Manager (Version 5.3, The Cochrane Collaboration, Copenhagen) and Stata (Version 12.0, Stata

Fig. 2 Trial sequential analysis of 5 trials comparing dupilumab with placebo for FEV$_1$. Trial sequential analysis of 7 groups (two trial contains two groups) illustrating that the cumulative z curve crossed both the conventional boundary and the trial sequential monitoring boundary, establishing sufficient and conclusive evidence and suggesting that further trials are not required. Using α = 0.05 (two-sided) and β = 0.20 (power of 80%) calculate that the optimal sample size was 1882 patients

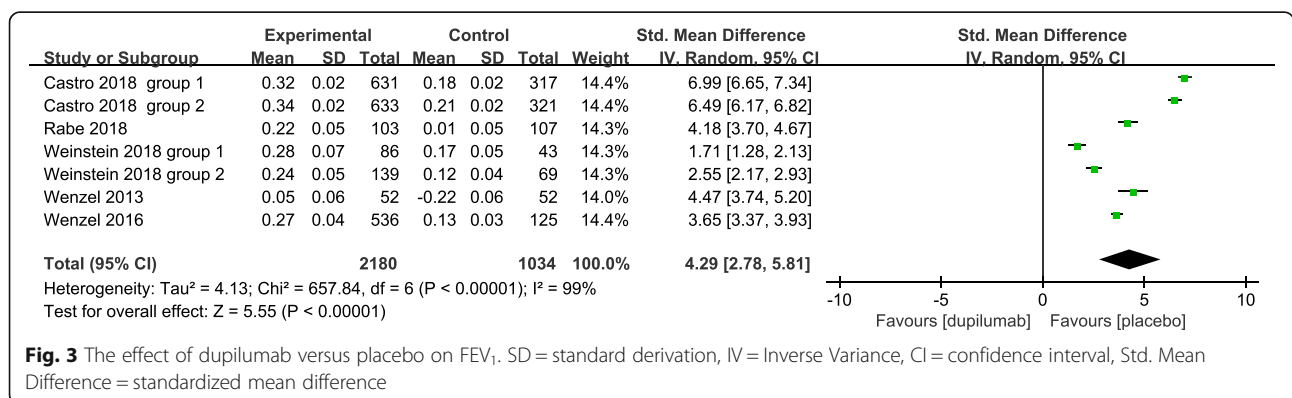Corporation, USA), and rendered statistical significance as *P*-value < 0.05.

Meta-analyses may cause type I errors because of sparse data and repetitive testing of accumulating data [22]. We performed trial sequential analysis (TSA) to assess the risk of type I errors, which can identify whether the evidence in a meta-analysis is reliable and authentic. If the cumulative z curve crosses the trial, the boundaries, and the required information size, the evidence is sufficient to reach a conclusion, a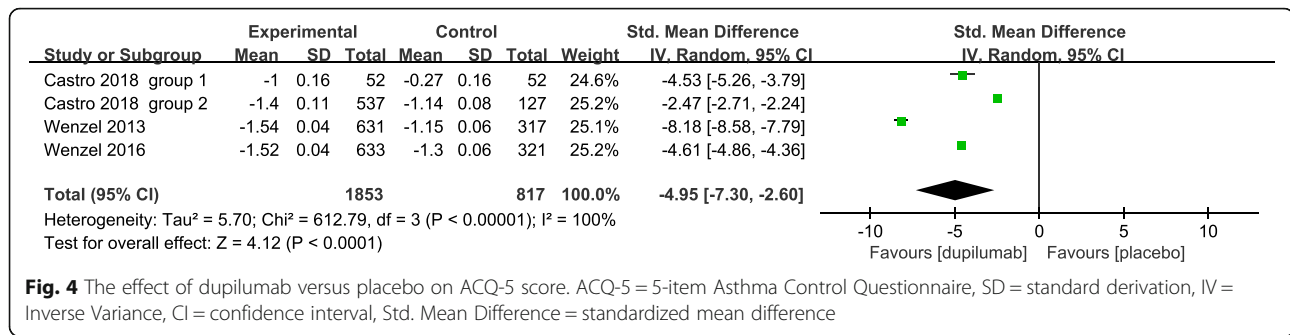nd no further studies are needed. We calculated the required information size for FEV$_1$ using α = 0.05 (2-sided) and β = 0.20 (power of 80%). TSA version 0.9 beta (http://www.ctu.dk/tsa) was applied for the analyses [23].

Results

Study identification

The initial database search resulted in 419 articles. After reviewing the titles and abstracts, 43 were found to be relevant for further detailed evaluation. Of these 38 were excluded as the population was wrong (*n* = 24), there

Fig. 3 The effect of dupilumab versus placebo on FEV$_1$. SD = standard derivation, IV = Inverse Variance, CI = confidence interval, Std. Mean Difference = standardized mean difference

Fig. 4 The effect of dupilumab versus placebo on ACQ-5 score. ACQ-5 = 5-item Asthma Control Questionnaire, SD = standard derivation, IV = Inverse Variance, CI = confidence interval, Std. Mean Difference = standardized mean difference

was no placebo control ($n = 4$), or data were unavailable ($n = 10$). Thus, 5 RCTs were included in the meta-analysis [15, 24–27] (Fig. 1).
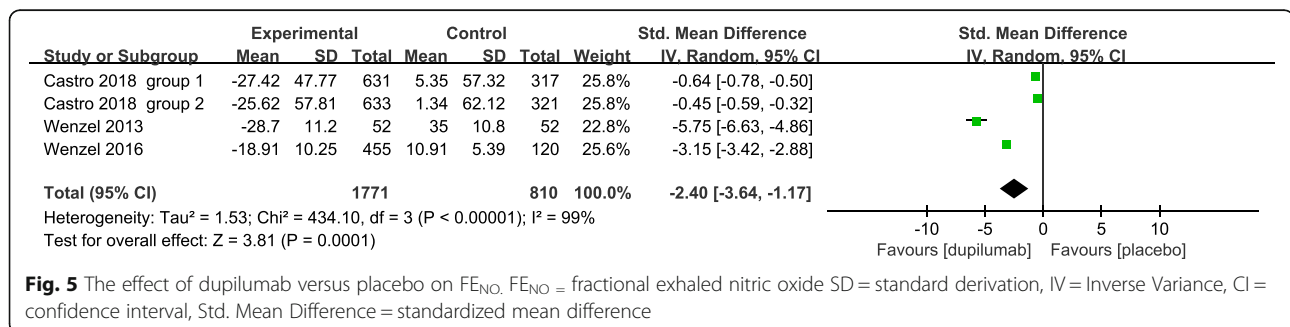
Study characteristics

We enrolled 5 studies with 3369 patients (Table 1). The sample sizes ranged from 52 to 632 subjects. A single intervention group (dupilumab 300 mg qw and 300 mg q2w) was presented in 2 trials, and the remaining studies included 2 or more interventions (dupilumab 200 mg q2w, 200 mg q4w, 300 mg q2w, 300 mg q4w). Outcome reporting varied among the trials. FEV_1 was reported in 5 studies [15, 24–27]. Severe asthma exacerbations rate was reported in 4 trials [15, 24–26]. ACQ-5 scores, FE_{NO}, and AM and PM asthma symptom scores were reported in 3 trials [15, 26, 27]. AQLQ was reported in 2 trials [15, 26].

Trial sequential analysis

TSA found that the optimal sample size required for reliable detection of a reasonable effect of dupilumab treatment on FEV_1 of asthma was 1882 participants; the number of patients included in our study far exceeded this number. TSA presented that the cumulative z curve crossed both the conventional boundary and the sequential monitoring boundary, which indicated that the cumulative evidence is reliable and authentic. Therefore, further studies were not needed (Fig. 2).

Efficacy

We assessed severity measures for efficacy including lung function (FEV_1), ACQ-5 score, FE_{NO}, AM and PM asthma symptom scores, severe asthma exacerbation rate, and quality of life (AQLQ). Overall, our studies illustrated significant improvement in the efficacy in the treatment of asthma with the use of dupilumab in terms of all clinical indexes. The pooled analyses indicated that dupilumab treatment significantly improved FEV_1 (SMD = 4.29, 95% CI: 2.78 to 5.81, $P < 0.001$). However, there was a high level of heterogeneity ($I^2 = 99\%$, $P < 0.001$) (Fig. 3), with no evidence of publication bias (Egger's test $P = 1.00$; Begg's test $P = 0.61$). In terms of ACQ-5 scores and FE_{NO}, our meta-analysis showed that dupilumab administration significantly decreased the ACQ-5 score and FE_{NO} (SMD = -4.95, 95% CI: -7.30 to -2.60, $P < 0.001$; SMD = -2.40, 95% CI: -3.64 to -1.17, $P < 0.001$, respectively), with high heterogeneity ($I^2 = 100\%$, $P < 0.001$) (Figs. 4 and 5), but no publication bias (Egger's test $P = 0.73$; Begg's test $P = 0.52$; Egger's test $P = 0.68$; Begg's test $P = 0.58$, respectively). Similar efficacy was observed in terms of the AM and PM asthma symptom score. Compared with placebo, dupilumab resulted in a greater reduction in the AM and PM asthma symptom scores (SMD = -5.09, 95% CI: -6.40 to -3.77, $P < 0.001$; SMD = -4.92, 95% CI: -5.98 to -3.86, $P < 0.001$, respectively), with high

Fig. 5 The effect of dupilumab versus placebo on FE_{NO}. FE_{NO} = fractional exhaled nitric oxide SD = standard derivation, IV = Inverse Variance, CI = confidence interval, Std. Mean Difference = standardized mean difference
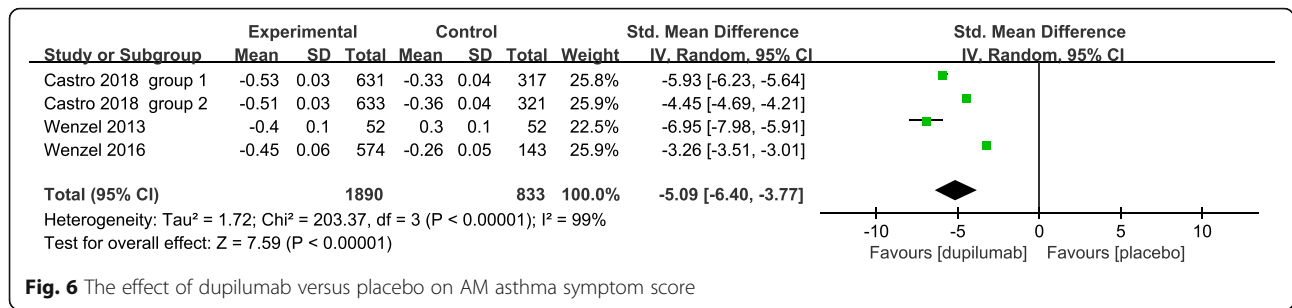
Fig. 6 The effect of dupilumab versus placebo on AM asthma symptom score

heterogeneity (I^2 = 99%, $P < 0.001$; I^2 = 98%, $P < 0.001$, respectively) (Figs. 6 and 7), and no publication bias (Egger's test $P = 0.73$; Begg's test $P = 0.51$). Additionally, dupilumab treatment was associated with a significant reduction in severe asthma exacerbation risk (RR = 0.73; 95% CI: 0.67 to 0.79; $P < 0.001$) (Fig. 8), without heterogeneity among studies (I^2 = 0%, P = 0.59), or publication bias (Egger's test $P = 0.98$; Begg's test, $P = 0.62$). For AQLQ, our analysis demonstrated that dupilumab treatment significantly increased AQLQ scores (SMD = 4.39, 95% CI: 1.44 to 7.34, P = 0.004), with high heterogeneity (I^2 = 100%, $P < 0.001$) (Fig. 9), and no publication bias (Egger's test, $P = 0.27$; Begg's test, $P = 0.07$).

Safety
All studies presented adverse events and dupilumab was relatively tolerated. The overall frequency of adverse events was similar in dupilumab-treated (79.2%) and placebo-treated (78.6%) patients (RR = 1.0; 95% CI: 0.96 to 1.04; $P = 0.94$), with no heterogeneity (I^2 = 0%, $P = 0.59$) (Fig. 10) and no publication bias (Egger's test $P = 1.00$; Begg's test, $P = 0.69$). The incidence of serious adverse events was relatively low in the dupilumab treatment group (2–8.7%). Common adverse events were injection-site reactions, upper respiratory tract infection, headache, nasopharyngitis, bronchitis, and sinusitis (Table 2).

Quality of the individual studies and subgroup analyses
All trials had a low risk of bias in terms of the 6 domains (Fig. 11). The publication bias of trials was estimated by visual inspection of the funnel plot and Egger's test, and there was no publication bias (Fig. 12, $P = 1.00$). According to the funding source, subgroup analyses were performed to assess sponsorship biases. Unfortunately, all studies were funded by a pharmaceutical company (Sanofi or Regeneron Pharmaceuticals). Thus, the results should be expounded with caution. In order to examine the source of heterogeneity, subgroup analyses were conducted for FEV_1 and ACQ-5 scores. The studies were stratified in terms of the effects model, region of trial, sample size, treatment duration, blood eosinophil count, and sources of funding, but no significant difference was found between groups in terms of FEV_1 and ACQ-5 scores (Table 3).

Discussion
To our knowledge, this is the first meta-analysis and comparison of all published data of RCTs on the use of dupilumab for the treatment of uncontrolled asthma. Our study indicated that dupilumab treatment was relatively tolerated and could significantly improve FEV_1 and quality of life, and reduced the disease symptom score and severe exacerbations risk in patients with uncontrolled asthma.
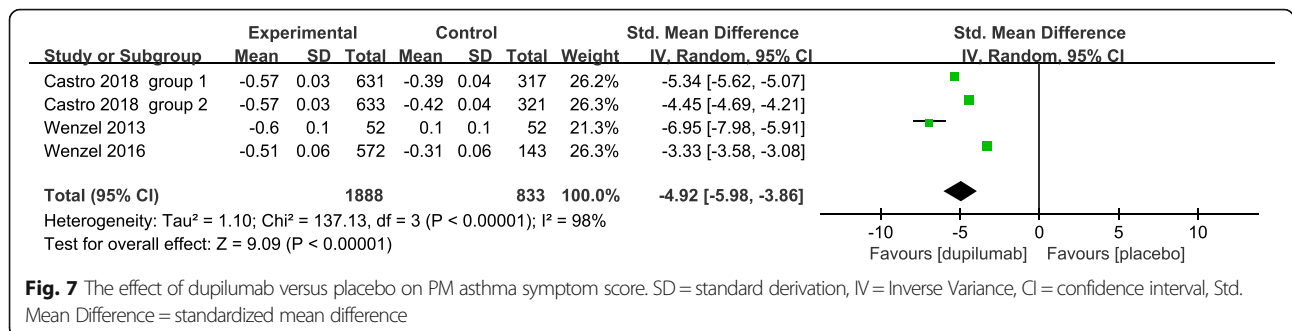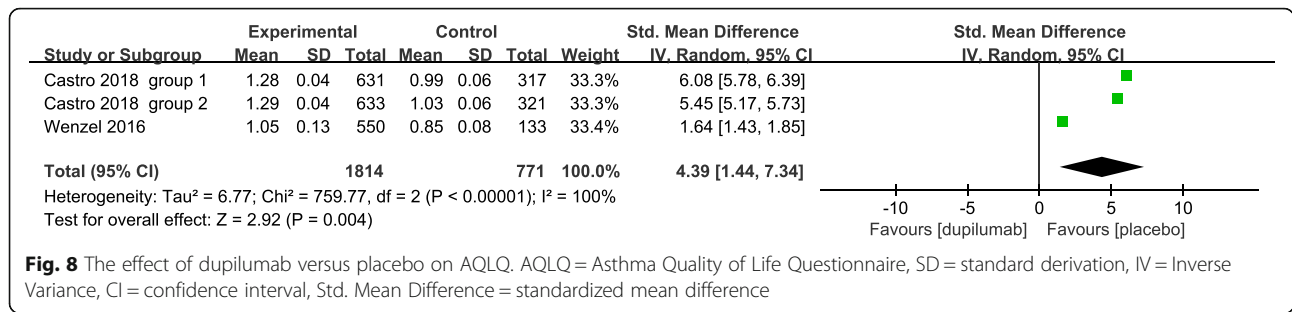

Fig. 7 The effect of dupilumab versus placebo on PM asthma symptom score. SD = standard derivation, IV = Inverse Variance, CI = confidence interval, Std. Mean Difference = standardized mean difference

Study or Subgroup	Experimental			Control			Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Castro 2018 group 1	1.28	0.04	631	0.99	0.06	317	33.3%	6.08 [5.78, 6.39]	
Castro 2018 group 2	1.29	0.04	633	1.03	0.06	321	33.3%	5.45 [5.17, 5.73]	
Wenzel 2016	1.05	0.13	550	0.85	0.08	133	33.4%	1.64 [1.43, 1.85]	
Total (95% CI)			**1814**			**771**	**100.0%**	**4.39 [1.44, 7.34]**	

Heterogeneity: Tau² = 6.77; Chi² = 759.77, df = 2 (P < 0.00001); I² = 100%
Test for overall effect: Z = 2.92 (P = 0.004)

-10   -5   0   5   10
Favours [dupilumab]   Favours [placebo]

Fig. 8 The effect of dupilumab versus placebo on AQLQ. AQLQ = Asthma Quality of Life Questionnaire, SD = standard derivation, IV = Inverse Variance, CI = confidence interval, Std. Mean Difference = standardized mean difference
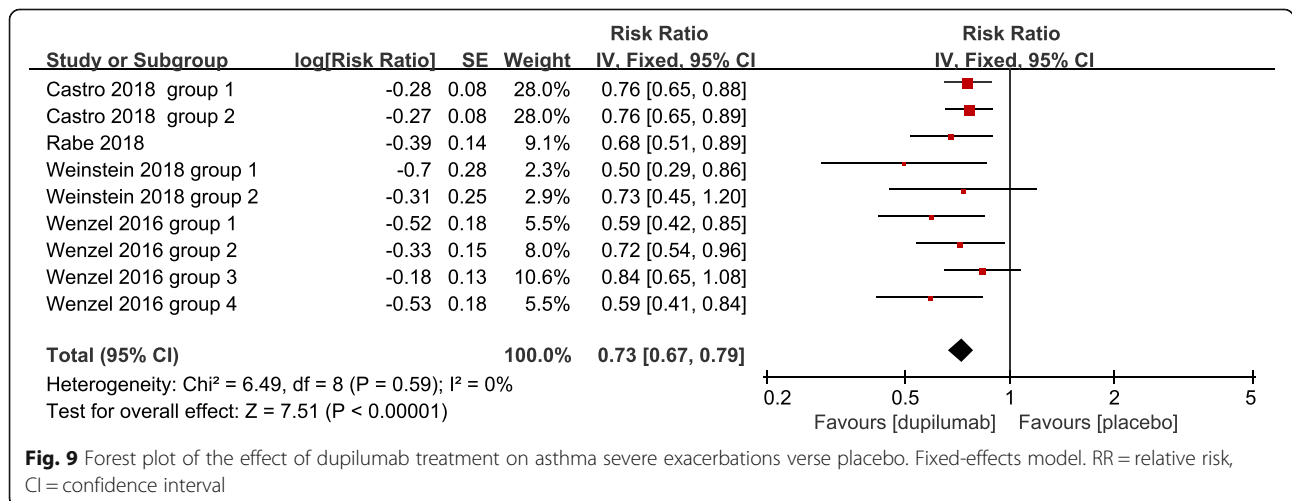
Asthma is a heterogeneous disease [1]. Previous studies have indicated that the Th2 cytokines IL-4 and IL-13 play a part in asthma [28, 29]. Dupilumab is an IL-4R antagonist that inhibits the IL-4 and IL-13 signaling pathway. Several clinical trials have been performed evaluating the effect of dupilumab in uncontrolled asthma. However, the evidence was insufficient to allow sound conclusions to be drawn, because the sample sizes varied; therefore, further analyses were necessary.

Based on pooled analyses, we found that dupilumab could significantly improve FEV_1 in patients with uncontrolled asthma. The clinical relevance of this finding may be clinically important, suggesting a potential effect of dupilumab on airway remodeling. However, a previous study [24] failed to show a significant effect on lung function as compared with placebo, which may be attributed to the small sample size and unselected population of patients with asthma. Compared to the previous study, we identified a selected population of patients with uncontrolled asthma. Moreover, we performed TSA to estimate the required information size for analysis, which can decrease the risk of random errors. Thus, our results may be more plausible. In addition, the different outcomes between our study and the previous trial suggested that dupilumab may be valid only in a targeted subgroup with uncontrolled asthma.

Three trails [15, 26, 27] showed that dupilumab could significantly reduce ACQ-5 scores and asthma symptom scores, which was consistent with our findings. AQLQ is a disease-specific health-related quality of life instrument that contains 32 items has been proven to be responsive in before–after studies and in clinical trials [30]. In our study, we used the AQLQ score to assess the quality of life of patients. Dupilumab treatment significantly improved AQLQ score in patients with uncontrolled asthma, this result was consistent with those of previous reviews. However, the mean change in AQLQ was less than the minimally important clinical difference of 0.5 units [31]. Thus, the relation of this finding to patients may not be clinically significant.

Given that nitric oxide (NO)-synthase activity and NO production are promoted by IL-13, FE_{NO} levels can be used as a biomarker of Th2 inflammation and of IL-13
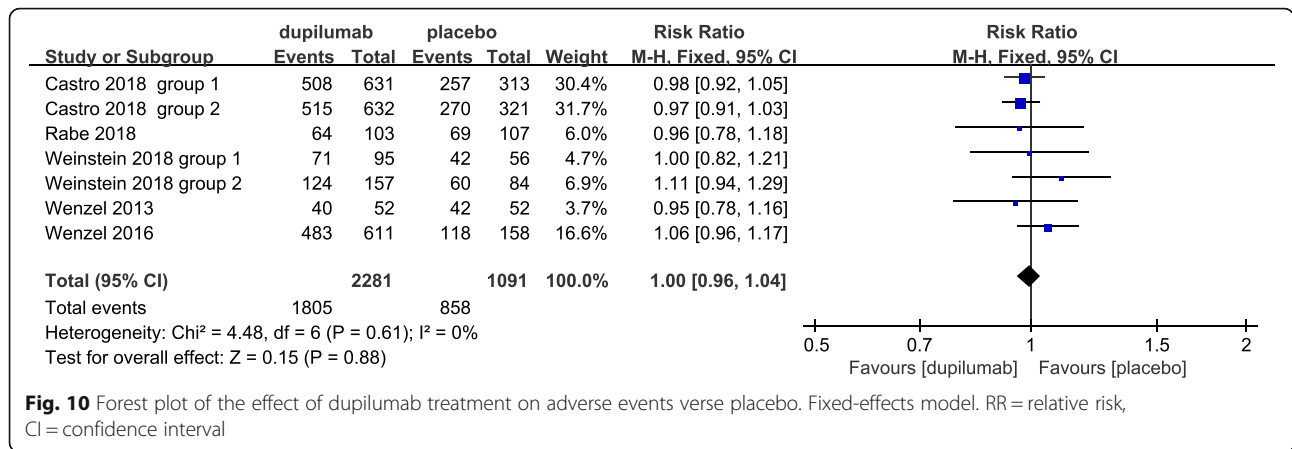
Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Castro 2018 group 1	-0.28	0.08	28.0%	0.76 [0.65, 0.88]	
Castro 2018 group 2	-0.27	0.08	28.0%	0.76 [0.65, 0.89]	
Rabe 2018	-0.39	0.14	9.1%	0.68 [0.51, 0.89]	
Weinstein 2018 group 1	-0.7	0.28	2.3%	0.50 [0.29, 0.86]	
Weinstein 2018 group 2	-0.31	0.25	2.9%	0.73 [0.45, 1.20]	
Wenzel 2016 group 1	-0.52	0.18	5.5%	0.59 [0.42, 0.85]	
Wenzel 2016 group 2	-0.33	0.15	8.0%	0.72 [0.54, 0.96]	
Wenzel 2016 group 3	-0.18	0.13	10.6%	0.84 [0.65, 1.08]	
Wenzel 2016 group 4	-0.53	0.18	5.5%	0.59 [0.41, 0.84]	
Total (95% CI)			**100.0%**	**0.73 [0.67, 0.79]**	

Heterogeneity: Chi² = 6.49, df = 8 (P = 0.59); I² = 0%
Test for overall effect: Z = 7.51 (P < 0.00001)

0.2   0.5   1   2   5
Favours [dupilumab]   Favours [placebo]

Fig. 9 Forest plot of the effect of dupilumab treatment on asthma severe exacerbations verse placebo. Fixed-effects model. RR = relative risk, CI = confidence interval

Study or Subgroup	dupilumab		placebo		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Castro 2018 group 1	508	631	257	313	30.4%	0.98 [0.92, 1.05]	
Castro 2018 group 2	515	632	270	321	31.7%	0.97 [0.91, 1.03]	
Rabe 2018	64	103	69	107	6.0%	0.96 [0.78, 1.18]	
Weinstein 2018 group 1	71	95	42	56	4.7%	1.00 [0.82, 1.21]	
Weinstein 2018 group 2	124	157	60	84	6.9%	1.11 [0.94, 1.29]	
Wenzel 2013	40	52	42	52	3.7%	0.95 [0.78, 1.16]	
Wenzel 2016	483	611	118	158	16.6%	1.06 [0.96, 1.17]	
Total (95% CI)		2281		1091	100.0%	1.00 [0.96, 1.04]	
Total events	1805		858				

Heterogeneity: Chi² = 4.48, df = 6 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)

0.5　0.7　1　1.5　2
Favours [dupilumab]　Favours [placebo]

Fig. 10 Forest plot of the effect of dupilumab treatment on adverse events verse placebo. Fixed-effects model. RR = relative risk, CI = confidence interval

levels in the bronchial mucosa [32]. Therefore, FE_{NO} levels could decrease after treatment with anti-IL-4/13 therapy [33]. The current meta-analysis further confirmed this theory: our study showed a significantly decrease in FE_{NO} levels after dupilumab treatment. Similarly, all previous trials of dupilumab treating uncontrolled asthma observed a reduction in the FE_{NO}

Fig. 11 Risk of bias summary of included studies summary

level, which is consistent with the mechanism of action of dupilumab.

Severe asthma exacerbations are related to substantial mortality [34]. Reducing asthma exacerbation risk is a key target of disease management. The part of Th2 inflammation is about 50% of asthmatic patients, in whom proinflammatory cytokines abnormally product, such as IL-4, IL-5, and IL-13, which induce IgE synthesis and eosinophilic inflammation [35]. Trials using specific inhibitors have indicated a relation between eosinophils and the pathogenesis of asthma exacerbations [36, 37]. Therefore, it is hypothesized that anti-IL-4 and anti-IL-13 therapies could decrease asthma exacerbation by inhibiting eosinophilic and airway inflammation. In further sustain of this concept, our study showed a significant reduction in severe exacerbation rates with dupilumab treatment. The improvements in asthma-related quality of life with dupilumab treatment may contribute to preventing severe asthma exacerbations.

The whole safety profile of dupilumab was equivalent to that of placebo in all RCTs, and the common adverse events were injection-site reactions, upper respiratory tract infection, headache, nasopharyngitis, bronchitis, and sinusitis. Four trials [15, 25–27] showed that the rates of upper respiratory tract infection in the dupilumab-treated group were low and similar to placebo group. However, all RCTs included revealed that the incidence of injection-site reactions was slightly higher in the dupilumab regimens. Therefore, more data are required to support the safety profile of dupilumab in terms of injection-site reactions.

This meta-analysis has some shortcomings. First, the severity of uncontrolled asthma and baseline therapy varied among studies; thus, it is impossible to probe the impact of these factors on results. Second, significant heterogeneity existed among trials evaluating FEV1, ACQ-5 score, FE_{NO}, and AQLQ, possible
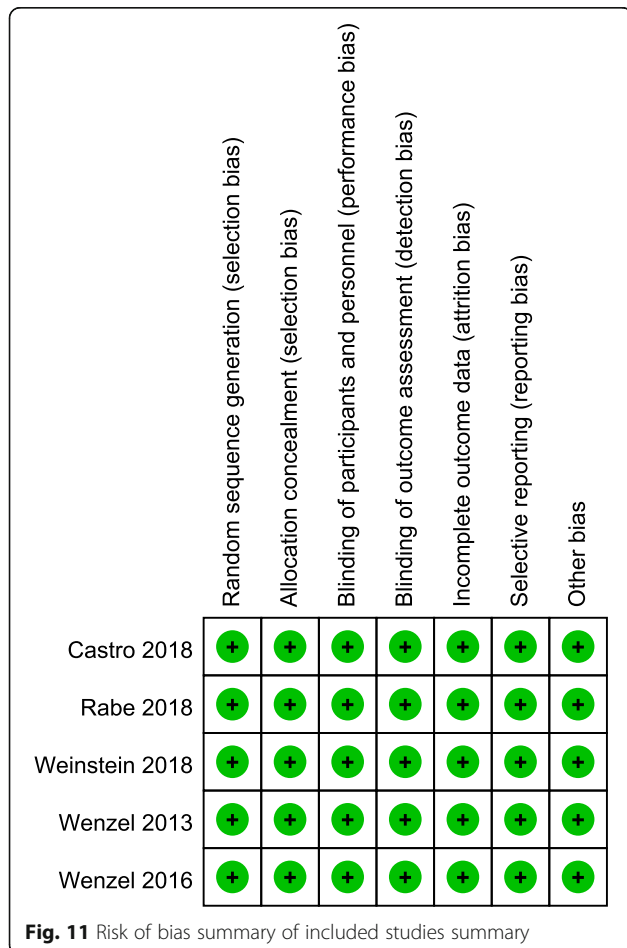
Table 2 Summary of adverse events in dupilumab treatment arm

Event	Wenzel 2013 [27]	Wenzel 2016 [15]	Castro 2018 [26]	Rabe 2018 [25]	Weinstein 2018 [24]
Any adverse event	42(80.8)	483(79.1)	1023(81.0)	64 (62.1)	195 (78.3)
Serious adverse event	1 (2.0)	45 (7.4)	104 (8.2)	9 (8.7)	15 (6.0)
Any adverse event leading to death	NM	2(<0.1)	5 (0.4)	0	0
Study discontinuation owing to treatment-emergent adverse event	3 (5.8)	27 (4.4)	63 (5.0)	1 (1.0)	8 (3.0)
Most common adverse events					
Injection-site reactions	15 (28.8)	79 (12.9)	212 (16.8)	9 (8.7)	60 (24.1)
Upper respiratory tract infection	7 (13.5)	216 (35.4)	146 (11.6)	NM	NM
Viral upper respiratory tract infection	3 (5.8)	83 (13.6)	230 (18.2)	9 (8.7)	NM
Headache	6 (11.5)	62 (10.1)	86 (6.8)	NM	NM
Nasopharyngitis	7 (13.5)	59 (9.7)	NM	NM	NM
Bronchitis	NM	51 (8.3)	144 (11.4)	7 (6.8)	NM
Sinusitis	1 (2.0)	36 (5.9)	62 (4.9)	7 (6.8)	NM

Note: Data are n (%)
Abbreviations: NM not mentioned

sources of heterogeneity might include different geographic regions and races. Third, we combined 2 or 3 intervention groups into a single group according to the Cochrane handbook, regardless of differences in intervention dosage, which made it hard to determine the optimal dose. Last, as all the RCTs involved the pharmaceutical industry, the positive outcomes should be expounded cautiously. Our study also had some strengths; for instance, our patient selection was highly consistent, and all trials were of high quality,

such that the internal validity of our meta-analysis was high.

Conclusions

The current meta-analysis demonstrated that dupilumab treatment was relatively tolerated and significantly improved FEV_1, symptoms, asthma control, and quality of life, and reduced severe exacerbation risk in patients with uncontrolled asthma. Thus, dupilumab may be effective and safe for the treatment of uncontrolled
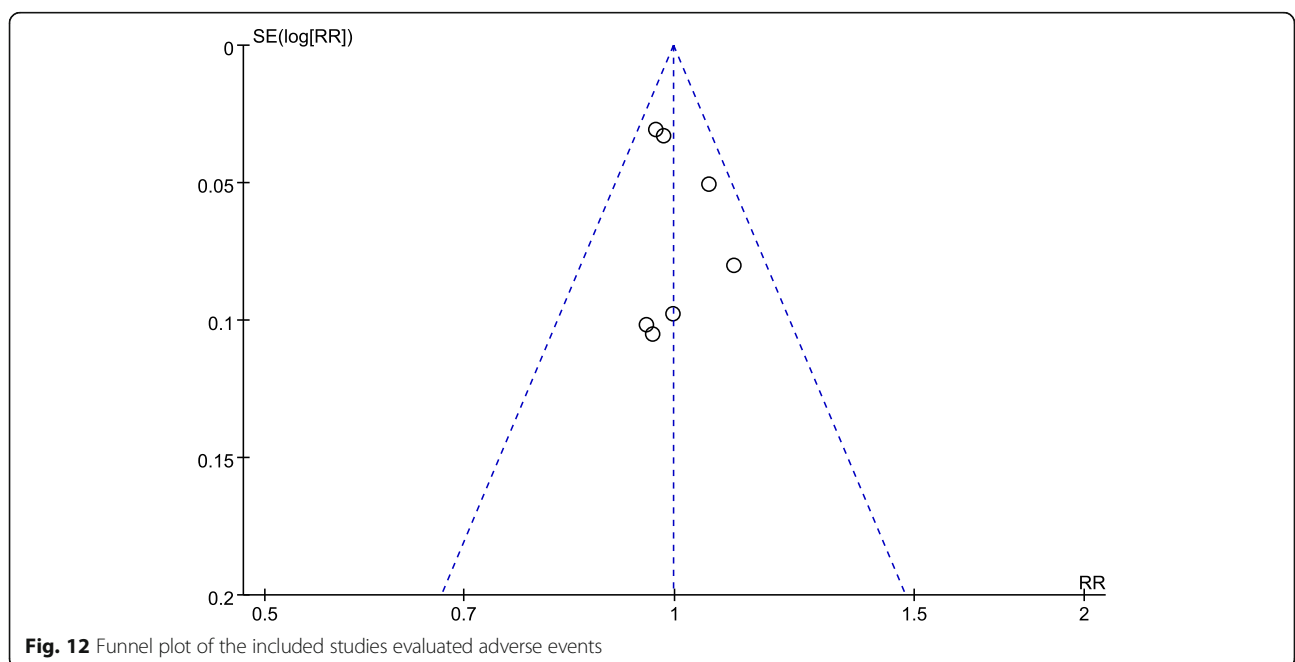

Fig. 12 Funnel plot of the included studies evaluated adverse events

Table 3 Subgroup analysis and sensitivity analyses of FEV$_1$ and ACQ-5 scores in RCTs

Stratification Subgroup analysis	FEV$_1$				ACQ-5 scores			
	No. of Patients (trials)	SMD (95% CI)	P Value	I$_2$, %	No. of Patients (trials)	SMD (95% CI)	P Value	I$_2$, %
Effects model								
Random-effects model	3218 (7)	4.29 (2.78 to 5.81)	< 0.001	99	2670 (4)	−4.95(−7.30 to −2.60)	< 0.001	100
Fixed effects model	3218 (7)	4.48 (4.32 to 4.62)	< 0.001	99	2670 (4)	−4.24(− 4.40 to − 4.09)	< 0.001	100
Region of study								
The US	104 (1)	4.47 (3.74 to 5.20)	< 0.001	–	104 (1)	−4.53(−5.26 to −3.79)	< 0.001	–
Multinational	3114 (6)	4.31 (2.85 to 5.97)	< 0.001	99	2566 (3)	−5.09(−7.29 to −2.25)	< 0.001	100
No. of subjects								
< 150	651 (4)	3.21 (1.98 to 4.43)	< 0.001	96	104 (1)	−4.53(−5.26 to −3.79)	< 0.001	–
≥150	2567 (3)	5.80 (3.86 to 7.74)	< 0.001	99	2566 (3)	−5.09(−7.29 to −2.25)	< 0.001	100
Treatment duration								
< 50 weeks	1316 (4)	3.35 (2.36 to 4.34)	< 0.001	96	768 (2)	−3.47(−5.48 to −1.46)	< 0.001	96
≥50 weeks	1902 (2)	6.74 (6.25 to 7.23)	< 0.001	77	1902 (2)	−6.39(−9.89 to −2.89)	< 0.001	100
Blood eosinophil count								
< 300 eosinophils per μl	1536 (5)	5.56 (2.59 to 8.53)	< 0.001	99	388 (1)	−1.80(−2.08 to − 1.52)	< 0.001	–
≥300 eosinophils per μl	1269 (4)	2.05 (0.97 to 3.12)	< 0.001	98	380 (2)	−2.43(−6.52 to − 1.66)	< 0.001	99
Sources of funding								
Pharmaceutical company		4.29 (2.78 to 5.81)	< 0.001	99		−4.95(−7.30 to −2.60)	< 0.001	100
Non-pharmaceutical company	0 (0)	–	–	–	–	–	–	–

Abbreviations: *FEV1* forced expiratory volume in 1 s, *ACQ-5* 5-item Asthma Control Questionnaire

asthma. These results highlight the significance of selecting the population patient of asthma that could obtain clinical benefit from dupilumab. Injection-site reaction was the most frequently reported adverse event in all studies involving dupilumab treatment. Further long-term trials are required to determine the optimum dose of dupilumab for asthma.

Abbreviations
ACQ-5: 5-item Asthma Control Questionnaire; AQLQ: The Asthma Quality of Life Questionnaire; FE$_{NO}$: Fractional exhaled nitric oxide; FEV$_1$: Forced expiratory volume in 1 s; IgE: Immunoglobulin E; IL: Interleukin; NM: Not mentioned; NO: Nitric oxide; PEF: Peak expiratory flow; q1w: Once weekly; q2w: Every 2 weeks; q4w: Every 4 weeks; RCTs: Randomized, placebo-controlled studies; RR: Relative risk; SMD: Standard mean differences; Th2: T-helper-2-cell

Authors' contributions
X-FX and MZ performed the literature searches, selected the studies, analyzed the data and wrote the manuscript draft. H-XW and L-LF aided in the data analysis. DYC designed the study and revised manuscript.
All authors read and approved the final manuscript.

Ethics approval and consent to participate
For this type of study formal consent is not required.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interest.

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