

Article type : Letter to the Editor

Treatment-emergent Adverse Events in Dupilumab-treated Patients with Allergic Diseases: a Meta-analysis

To the Editor:

Allergic diseases such as asthma, chronic rhinosinusitis (CRS), atopic dermatitis (AD), allergic rhinitis, and eosinophilic esophagitis (EoE) affect more than 30% of the population,¹ with a dramatic increase² and a lack of effective treatments for recurrent or adverse effects of corticosteroids and immunosuppressants.^{3,4} Dupilumab is a monoclonal antibody that targets the IL-4 receptor alpha subunit and inhibits IL-4/IL-13 signaling, thus downregulating type-2 inflammatory responses.⁵ Currently, dupilumab has proven effectiveness in patients with serious allergic diseases.⁶⁻⁸ However, the evidence on safety of dupilumab is insufficient in allergic diseases. Therefore, we conducted a meta-analysis to assess the overall safety of dupilumab treatment by exploring the risk of treatment-emergent adverse event (TEAE) in patients with allergic diseases.

We carried out a systematic literature search of PubMed, Web of Science, EMBASE, and the Cochrane Library databases using the keywords such as “allergic disease”, “dupilumab” to identify randomized controlled trials (RCTs) of dupilumab therapy in patients with allergic diseases from inception to June 2020. Seventeen RCTs with a total of 7,578 participants were finally eligible for inclusion in this meta-analysis through our literature search strategy (Figure S1). The characteristics of the included studies are listed in Table S1. A quality assessment of the 17 RCTs were shown in Figure S2. In addition, the points in the funnel plot of the included RCTs

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were almost symmetrically distributed (Figure S3), and Egger's tests showed there was no statistical difference in publication bias among the RCTs ($P = 0.467$). Sensitivity analyses of any TEAE, any serious TEAE, and any TEAE by removing each RCT suggest that no single study had a significant impact on the results (Figure S4).

A pooled analysis showed that the incidence of any serious TEAE was 223 of 4,923 (4.53%) patients receiving dupilumab treatment and 139 of 2,401 (5.79%) patients receiving placebo. Treatment of patients with dupilumab was associated with a 32% lower risk of any serious TEAE than with placebo (RR = 0.68; 95% CI, 0.50–0.94; $P = 0.02$; $I^2 = 30.28\%$; Figure 1A). Furthermore, there was no evidence of a difference in risk for any TEAE leading to death between dupilumab (11/4557, 0.24%) and the placebo group (3/2303, 0.13%; RR = 0.95; 95% CI, 0.40–2.24; $P = 0.91$; $I^2 = 0.00\%$; Figure 1B). Data on the occurrence of any TEAE during dupilumab treatment showed that patients receiving dupilumab treatment (3809/5050, 75.43%) did not have a higher risk of any TEAE compared with those receiving placebo (1921/2528, 75.99%; RR = 0.99; 95% CI, 0.96–1.02; $P = 0.56$; $I^2 = 14.08\%$; Figure 1C). The risk of any leading to permanent treatment discontinuation in patients receiving dupilumab treatment was similar to that in patients receiving placebo (RR = 0.78; 95% CI, 0.53–1.16; $P = 0.23$; $I^2 = 32.37\%$; Figure 1D). In the 17 RCTs, 14 common TEAEs were reported following dupilumab treatment. A meta-analysis revealed lower risks of skin infections in patients receiving dupilumab treatment than in those receiving placebo (RR = 0.56; 95% CI, 0.45–0.71; $P < 0.01$; $I^2 = 0.00\%$; Table 1). In addition, the risk of other common TEAEs (headache, nasopharyngitis, bronchitis, upper respiratory tract infection, back pain, influenza, urinary tract infection, rash, gastroenteritis, herpes viral infections) in patients receiving dupilumab treatment was similar to that in patients receiving placebo (all $P > 0.05$; Table 1). However, injection-site reactions (RR = 1.90; 95% CI, 1.50–2.40; $P < 0.01$; $I^2 = 37.69\%$), conjunctivitis (RR = 2.44; 95% CI, 1.82–3.26; $P < 0.01$; $I^2 = 0.00\%$) and eosinophilia (RR = 5.85; 95% CI, 2.57–13.28; $P < 0.01$; $I^2 = 0.00\%$) were both associated with a higher risk in the dupilumab group than in the placebo group (Table 1).

We next analyzed whether dupilumab can reduce the risk of developing other allergic diseases in patients with allergic disease. The pooled data for the risk of developing asthma in

patients with CRSwNP (2 RCTs) and AD (3 RCTs) demonstrated there was a 67% lower risk of developing asthma in patients that received dupilumab than in those that received placebo (RR = 0.33; 95% CI, 0.20–0.54; $P < 0.01$; $I^2 = 0.00\%$; Table 1). Meanwhile, among the five RCTs that included patients with allergic diseases such as asthma (3 RCTs) and AD (1 RCT), the risk of sinusitis was lower in patients that received dupilumab than in those that received placebo (RR = 0.60; 95% CI, 0.45–0.81; $P < 0.01$; $I^2 = 0.00\%$) (Table 1).

The present study examined the adverse events associated with dupilumab in various serious allergic diseases. Our result showed a lower risk for any serious TEAE in patients treated with dupilumab, suggesting that dupilumab does not increase the occurrence of serious adverse reactions. Further, an exacerbation of allergic diseases was observed in the placebo group, possibly because of a lack of effective treatment. The incidence of TEAEs leading to death, any TEAE and any leading to permanent treatment discontinuation was generally similar across the treatment groups, suggesting that dupilumab has a placebo-like safety profile. Further analysis the specific adverse events with significant differences between the dupilumab and placebo groups. The patients receiving dupilumab presented a lower risk of skin infections, which was consistent with an improvement in skin barrier integrity and function treated with dupilumab. Although injection-site reactions occurred more frequently in dupilumab group, most of studies were classified as mild and controllable. The higher incidence of conjunctivitis only appears in AD, not in other allergic diseases, which may be associated with the pre-existing ocular disorders in patients with AD. Since dupilumab downregulates type-2 inflammatory responses, it may cause the transition of chronic inflammation from the Th2 dominant pathway to the Th1 dominant pathway, which may be one of the reasons why dupilumab-induced conjunctivitis mainly manifested as Th1-mediated inflammation occurs more frequently in patients with AD. Studies have reported that the dupilumab related eosinophilia was transient, which mainly observed after treatment initiation, and rapidly declined after treatment withdrawal. It is speculated that since dupilumab inhibits the production of eotaxins mediated by IL-4 and IL-13, and then blocks eosinophil tissue migration, and finally results in a transient increase in blood eosinophil levels.

What's more, our result showed that dupilumab is associated with a lower risk of developing

other allergic diseases, such as asthma or sinusitis, indicated that dupilumab can effectively prevent the occurrence of other allergic diseases in patients with allergic disease and that it plays a defensive and protective role against allergic diseases. The mechanism for this may be that dupilumab suppresses type-2 immunity by blocking both IL-4 and IL-13 signaling and thereby inhibits the development of allergic responses.⁵ Dupilumab could therefore be a targeted therapy for the treatment of a broad range of allergic diseases. The limitation of this study was the short and diverse duration in follow-up which ranges from 16 weeks to 52 weeks. These trials might not be long enough to exclude uncommon adverse events. So long-term safety and efficacy of dupilumab for the treatment of allergic diseases remains to be evaluated.

In summary, dupilumab has an acceptable safety profile for the treatment of patients with allergic diseases and is associated with a low risk of developing other allergic diseases. However, the long-term safety and efficacy of dupilumab for the treatment of a broader range of allergic diseases must be evaluated in future clinical research.

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143 **Conflicts of interest**

144 The authors declare that there are no potential conflicts of interest.

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Table 1. The difference of risks of various treatment-emergent adverse events in the patients with allergic disease between those received dupilumab or placebo.

TEAEs	Number of studies	Treatment (dupilumab)		Control (placebo)		RR	95% CI	<i>P</i> value	I ² , %
		Event	Total patients	Event	Total patients				
Risks of common TEAEs									
Skin infection	7	141	2066	132	1035	0.56	0.45 to 0.71	< 0.01	0.00
Headache	14	384	4903	172	2387	1.04	0.86 to 1.26	0.66	6.23
Nasopharyngitis	14	512	3663	228	1777	1.06	0.92 to 1.23	0.42	0.00
Bronchitis	5	211	2345	116	1011	0.83	0.67 to 1.03	0.08	0.00
Upper respiratory tract infection	14	513	4486	233	2129	0.92	0.80 to 1.06	0.26	0.00
Back pain	6	81	2193	34	942	0.87	0.44 to 1.73	0.69	35.24
Influenza	5	137	2740	80	1296	0.83	0.52 to 1.32	0.43	36.35
Urinary tract infection	4	61	1971	35	829	0.68	0.44 to 1.03	0.07	0.00
Rash	3	74	708	14	195	1.11	0.66 to 1.87	0.68	0.00
Gastroenteritis	4	11	634	6	269	0.91	0.25 to 3.31	0.89	20.71
Herpes viral infections	8	123	2410	50	1134	1.11	0.79 to 1.56	0.56	0.00
Injection-site reaction	16	677	5029	176	2518	1.90	1.50 to 2.40	< 0.01	37.69
Conjunctivitis	8	233	1936	51	1149	2.44	1.82 to 3.26	< 0.01	0.00

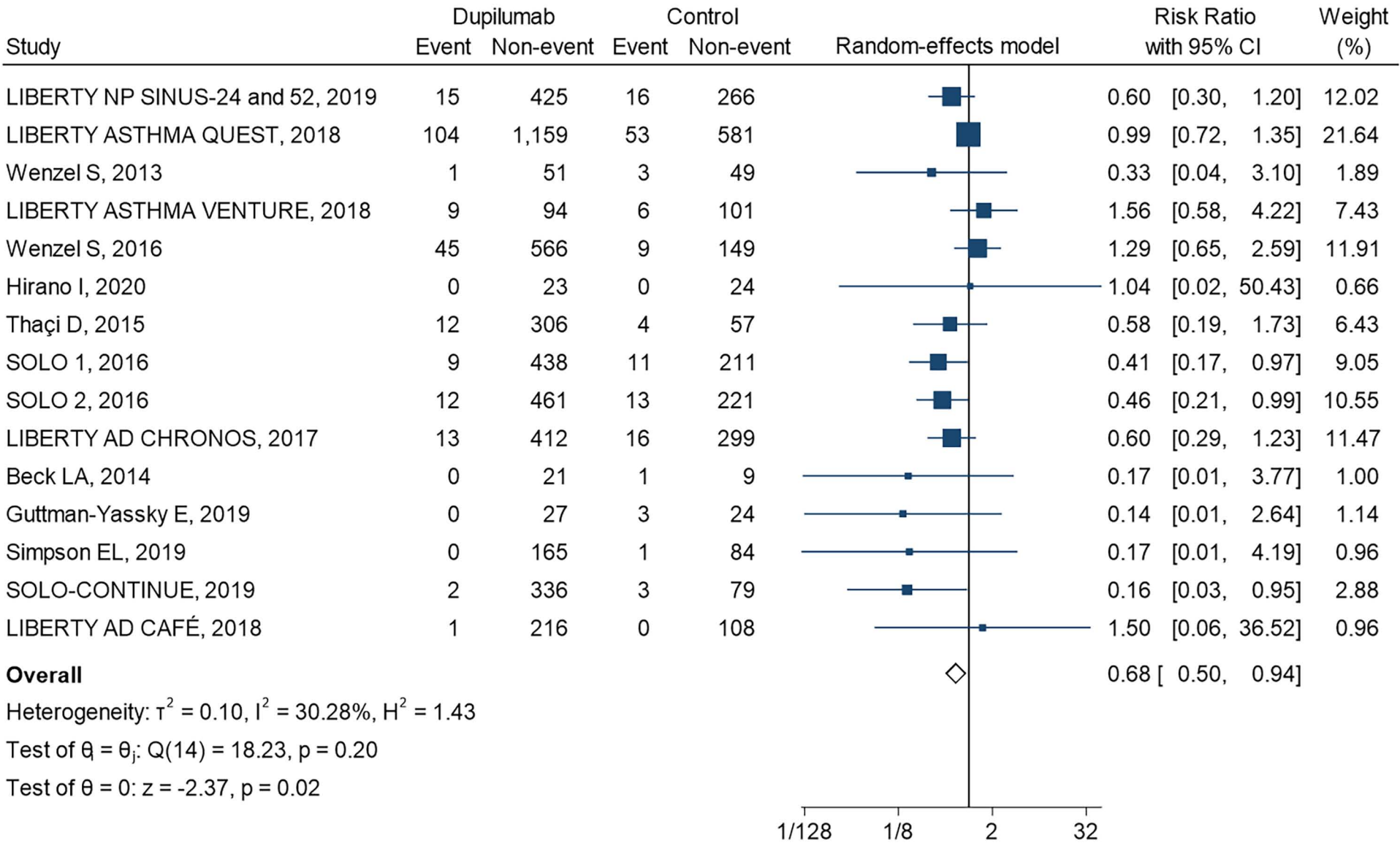
Eosinophilia	4	69	1832	6	1051	5.85	2.57 to 13.28	< 0.01	0.00
Risks of developing other allergic diseases									
Asthma	5	28	1450	48	817	0.33	0.20 to 0.54	< 0.01	0.00
Sinusitis	4	105	2264	74	926	0.60	0.45 to 0.81	< 0.01	0.00

TEAEs: treatment-emergent adverse events; RR: rate ratio; CI: confidence interval.

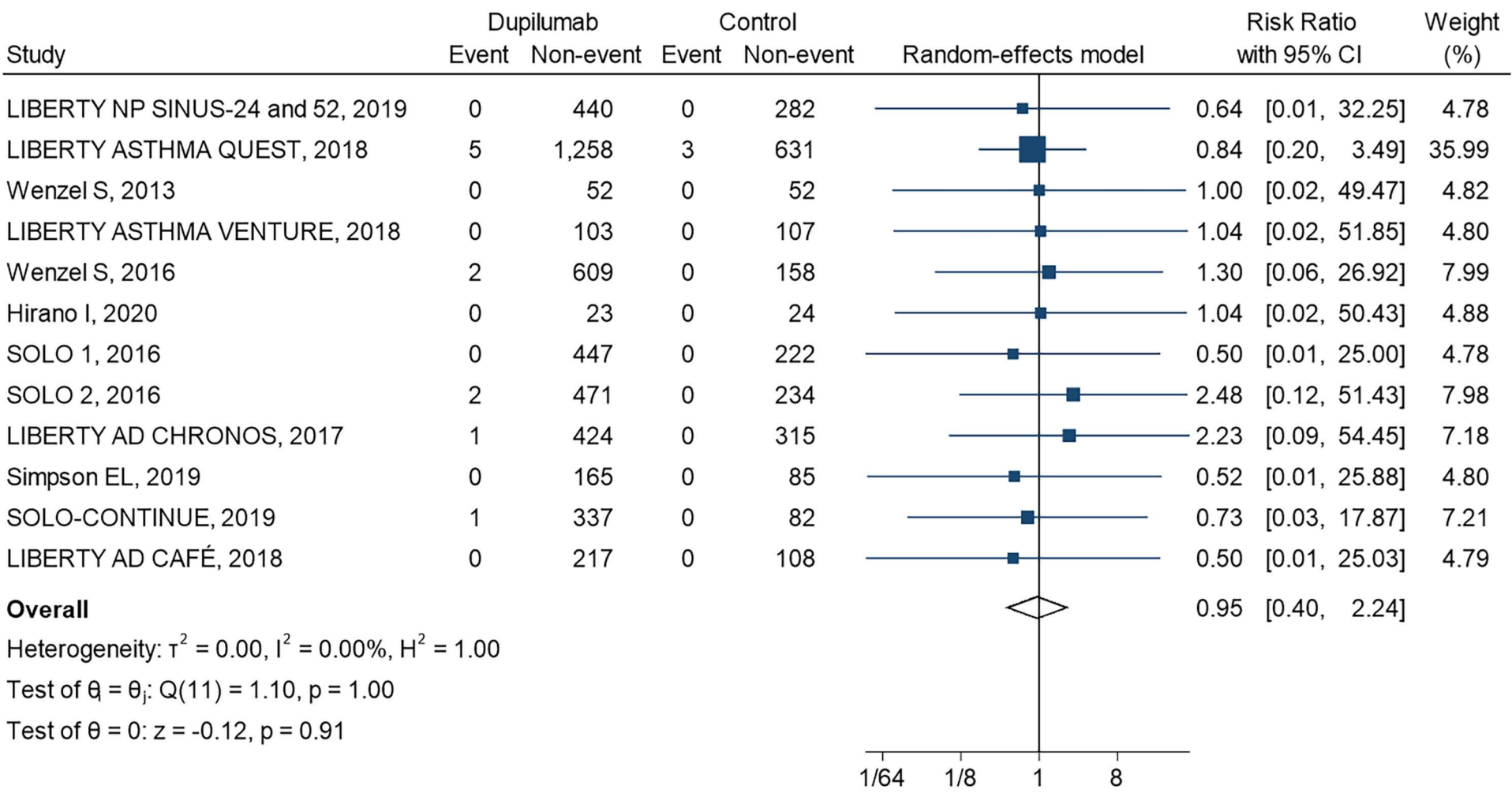
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Figure 1. Forest plot of the rate of any serious TEAE, any TEAE leading to death, any TEAE and any leading to permanent treatment discontinuation. Rates for any serious TEAE (A), any TEAE leading to death (B), any TEAE (C), and any leading to permanent treatment discontinuation (D) and their RR rates between dupilumab and placebo-treated patients with allergic diseases.

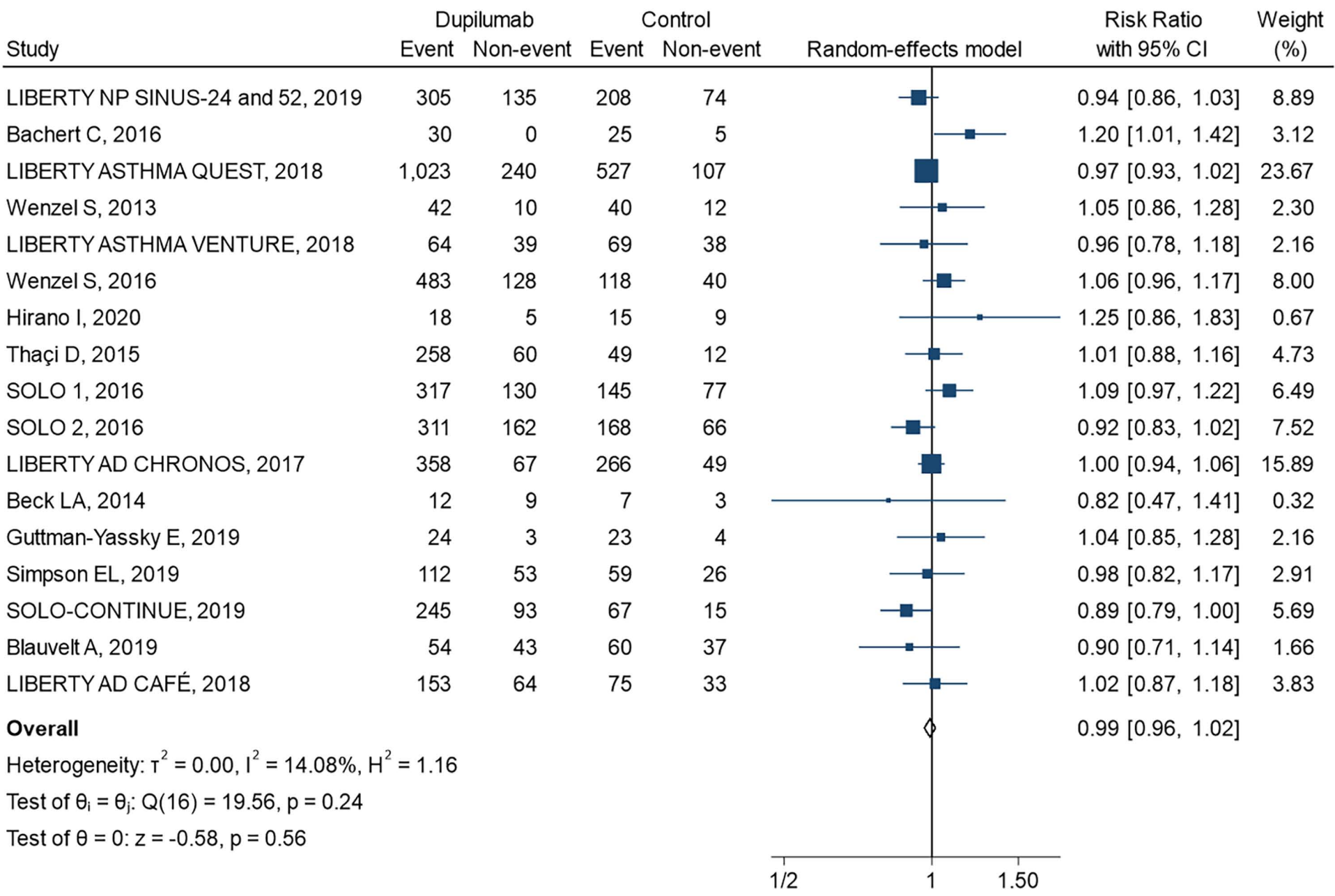
A Any serious TEAE



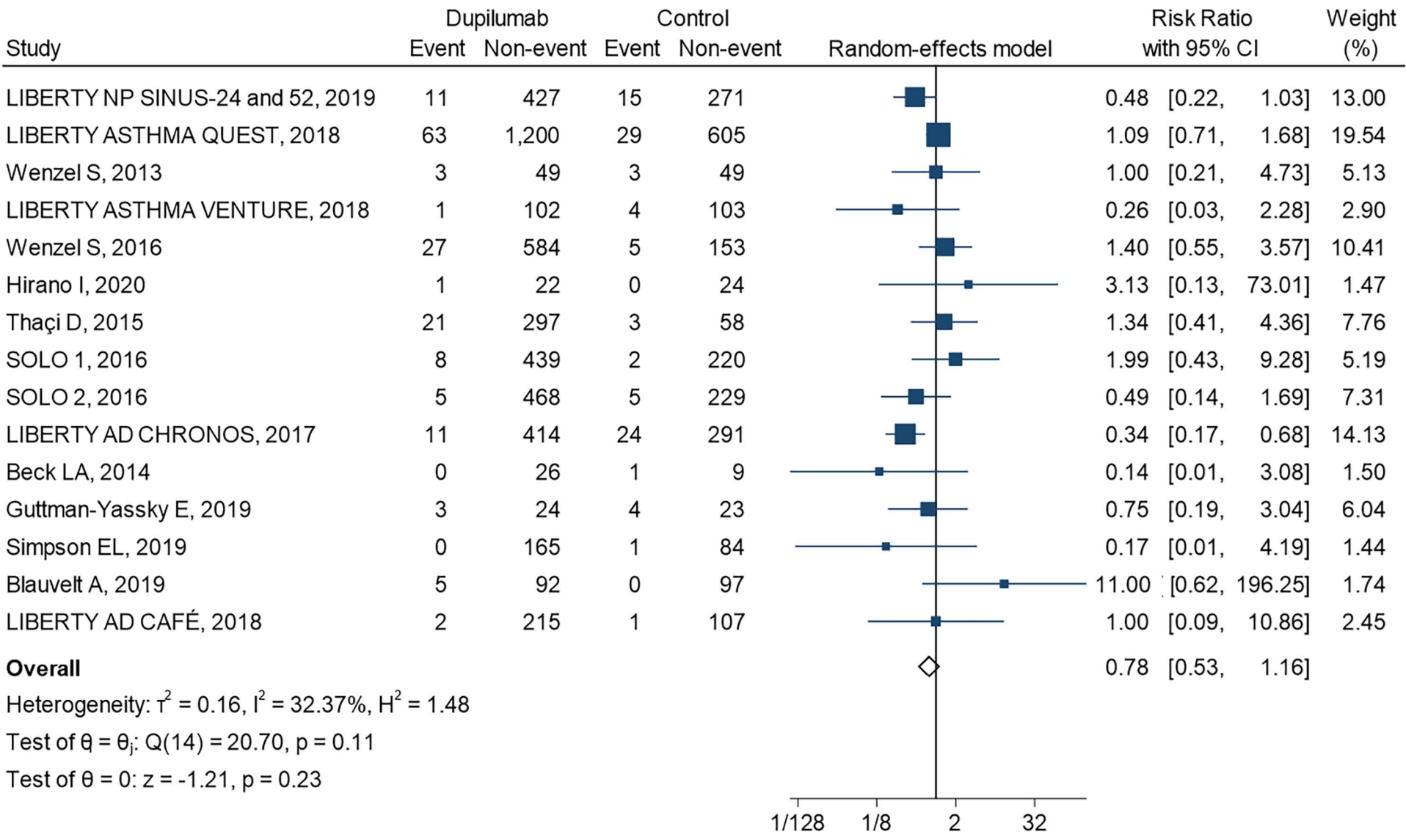
B Any TEAE leading to death



C Any TEAE



D Any leading to permanent treatment discontinuation



Online Supplementary File

Methods

This study was conducted in line with the Cochrane and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.¹

1 | Search strategy

We carried out a systematic literature search of PubMed, Web of Science, EMBASE, and the Cochrane Library databases using the keywords such as “allergic disease”, “dupilumab” to identify randomized controlled trials (RCTs) of dupilumab therapy in patients with allergic diseases from inception to June 2020. The detailed search strategies are listed in Table S1 (Additional Files).

2 | Inclusion and exclusion criteria

The following criteria were used for inclusion: (1) The population consisted of patients with allergic diseases such as allergic rhinitis, asthma, CRS, AD, EoE, and eczema; (2) Patients received dupilumab treatment in the experimental group or placebo in the control group; (3) The outcome of the study reported adverse events of treatment; (4) The study design was limited to RCTs. Case reports, review articles, basic research, comments, duplicate reports, and editorials were excluded.

3 | Study selection

All references were uploaded into the reference management software NoteExpress (v3.2.0.7535). All title and abstract reviews were independently checked by two researchers (XC and ML) against the inclusion criteria. If either reviewer felt that a study met the eligibility criteria, the full text of the study was examined. Any disagreements were resolved by group discussion to reach a consensus. Of these, 16 articles²⁻¹⁷ met the inclusion criteria.

4 | Quality assessment

The quality of the included RCTs was assessed by two reviewers (ZH and XL) independently, based on the seven categories in the Cochrane Risk of Bias (ROB) assessment tool.¹⁸ Then, based on these categories, the quality for each RCT was assessed by a consensus discussion amongst reviewers.

5 | Data extraction

Data were extracted independently by two reviewers (XC and ML) according to a predesigned standardized form. Any dispute over data was arbitrated by a third author (SW) or resolved by a group discussion to reach a consensus. The following information was extracted: first author, year of publication, types of allergic disease, design of the clinical trial, baseline characteristics of the patients, detailed usage and dosage of dupilumab, and therapeutic schedule. In addition, for the assessment of safety, any treatment-emergent adverse event (TEAE), any TEAE leading to death, and the incidence of other allergic diseases were all separately extracted from these studies.

6 | Statistical analysis

The statistical program Stata (version 16.0, StataCorp, College Station, Texas) and the R language (version 3.5.0.12) were used for statistical analysis. The results are shown as the risk ratio (RR) with 95% CIs and *P* values. Heterogeneity among studies was assessed using a standard chi-squared test, and significant inconsistency was indicated by $I^2 > 50\%$ and $P < 0.10$.¹⁹ Although lower I^2 were obtained in our analyses, a random-effects model was also conducted to estimate the pooled effects in order to decrease the possible impact of heterogeneity on the results. A sensitivity analysis by removing each study were used to assess its impact on the remaining meta-analysis. Evidence of publication bias was checked by funnel plots and Egger's test following Cochrane, but only if more than 10 available studies were conducted.²⁰

Table S1. Characteristics of the studies included in the meta-analysis.

Study, year	Types of allergic diseases	Design of RCT	Treatment (dupilumab) *	Control	Concomitant treatment	Age, year #		Male, %	White, %
						Treatment	Control		
LIBERTY NP SINUS-24 and 52, 2019	Severe CRSwNP	Phase III	300mg q2w(24)	Placebo	Intranasal corticosteroids	52 (42–61)		437 (60)	NA
Bachert C, 2016	CRSwNP	Phase II	300mg q2w(52); 300mg q2w(24) +300mg q4w(28)	Placebo	Intranasal corticosteroids	47±10	49±9	34 (57)	59 (98)
LIBERTY ASTHMA QUEST, 2018	M-to-S uncontrolled asthma	Phase III	200mg q2w(52); 300mg q2w(52);	Placebo	Inhaled corticosteroids + β2-agonist	48 ± 15		705 (37)	NA
Wenzel S, 2013	Asthma with elevated EOS	Phase II	300mg qw(12)	Placebo	Inhaled corticosteroids + β2-agonist	38±13	42±13	52 (50)	83 (80)
LIBERTY ASTHMA VENTURE, 2018	Severe Asthma	Phase III	300mg q2w(24);	Placebo	Oral glucocorticoid	51±13		83 (40)	NA
Wenzel S, 2016	Uncontrolled asthma	Phase II	200mg q2w/q4w(24)	Placebo	Inhaled corticosteroids + β2-agonist	49±13		286 (37)	607 (78)
Hirano I, 2020	Active EoE	Phase II	300mg qw(12);	Placebo	Proton pump inhibitors	33±9	36±13	23 (49)	44 (94)
Thaçi D, 2016	M-to-S AD	Phase II	300mg qw/q2w/q4w(16); 200mg q2w(16); 100mg q4w(16)	Placebo	Opical emollient	37±12	37±13	234 (62)	NA
SOLO 1, 2016	AD	Phase III	300mg qw/q2w (16)	Placebo	Moisturizers	39 (27–51)	39 (27–51)	390 (58)	450 (67)
SOLO 2, 2016	AD	Phase III	300mg qw/ q2w (16)	Placebo	Moisturizers	35 (25–46)	35 (25–47)	408 (48)	489 (69)
LIBERTY AD CHRONOS, 2017	M-to-S AD	Phase III	300mg qw/q2w(52);	Placebo	Topical corticosteroids	34 (26–45)	34 (25–45)	446 (60)	490 (66)
Beck LA, 2014	M-to-S AD	Phase II	300mg qw(4);	Placebo	Topical corticosteroids	36±3	38±5	13 (42)	30 (97)
Guttman-Yassky E, 2019	AD	Phase II	200mg qw(16);	Placebo	Opical emollient	35 (27-50)	43 (34-49)	30 (56)	39 (72)
Simpson EL, 2019	M-to-S AD	Phase III	200mg q2w(16); 300mg q2w/q4w(16)	Placebo	Moisturizers	15±2		148 (59)	157 (63)
SOLO-CONTINUE, 2019	AD	Phase III	300mg qw/q2w/q4w/q8w (36)	Placebo	Moisturizers	36 (26-48)	37 (27-46)	227 (54)	298 (71)
Blauvelt A, 2019	M-to-S AD	Phase II	300mg qw(16)	Placebo	Topical corticosteroids	39±14	40±14	95 (49)	127 (65)
LIBERTY AD CAFÉ, 2018	AD	Phase III	300mg qw/q2w (16)	Placebo	Topical corticosteroids	38 (29–48)	38 (29–49)	199 (61)	313 (96)

RCT: Randomized clinical trial; CRSwNP: Chronic rhinosinusitis with nasal polyps; EoE: Eosinophilic esophagitis; AD: Atopic dermatitis; qw: every week; q2w: every two weeks; q4w: every four weeks; q8w: every eight weeks; ICS: Inhaled corticosteroids; M-to-S: Moderate-to-severe; EOS: eosinophil levels. * dosage and usage of subcutaneous injection dupilumab (duration). NA, not available; # Normally distributed data are shown as mean ± standard deviation, and non-normally distributed data are shown as median (interquartile range).

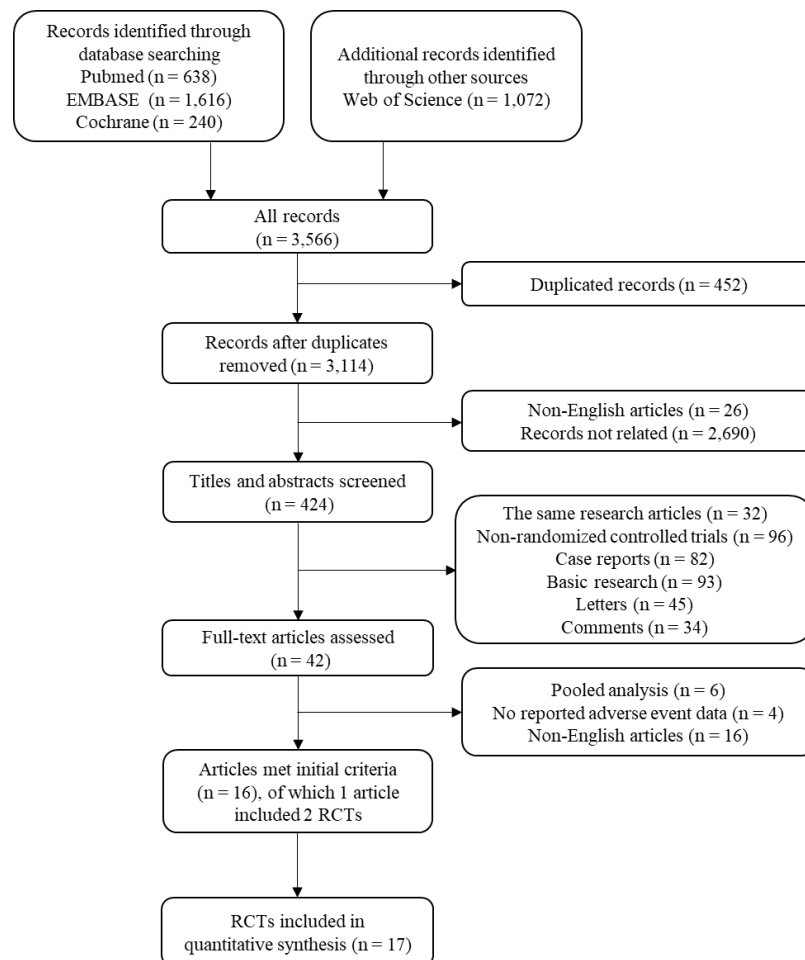


Figure S1. PRISMA flow diagram of the selection process in this study.

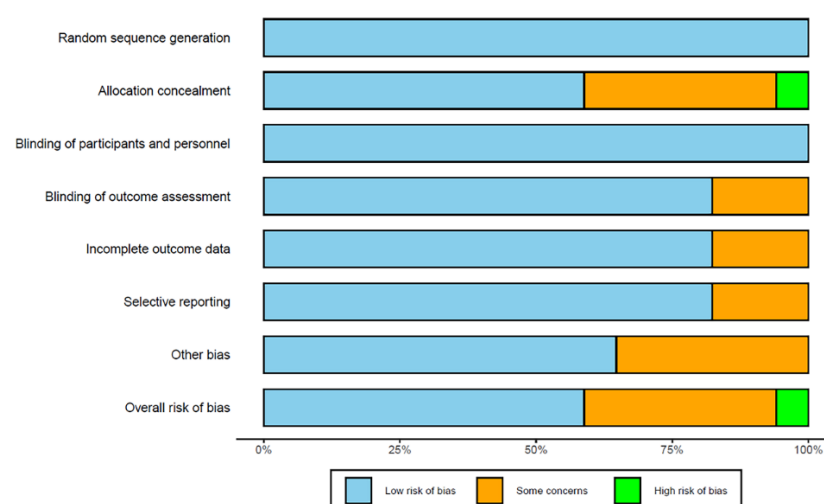


Figure S2. Assessment of the risk of bias for the 17 randomized controlled trials included in this study. A quality assessment revealed that 10 of the RCTs were judged to have a low risk of bias; six RCTs were viewed as having an unclear risk of bias, and the remaining one RCT was judged to have a high risk of bias.

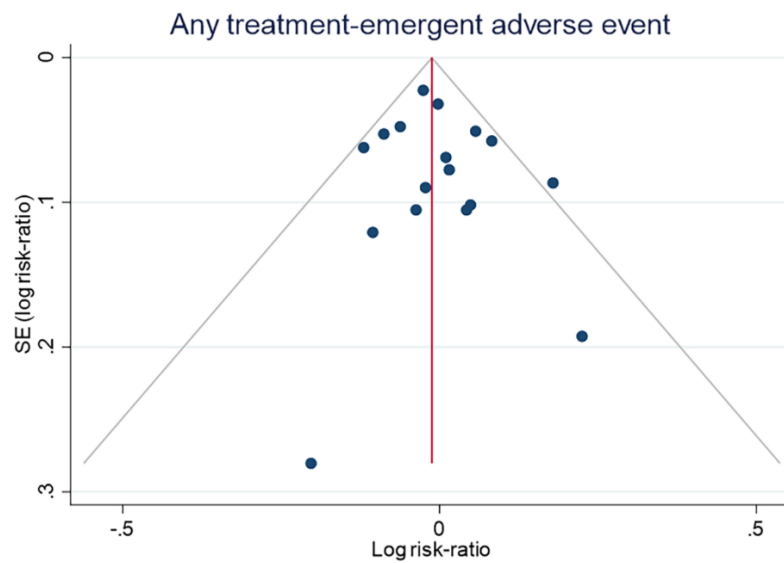


Figure S3. Funnel plot of any treatment-emergent adverse event for the 17 randomized controlled trials included in this study

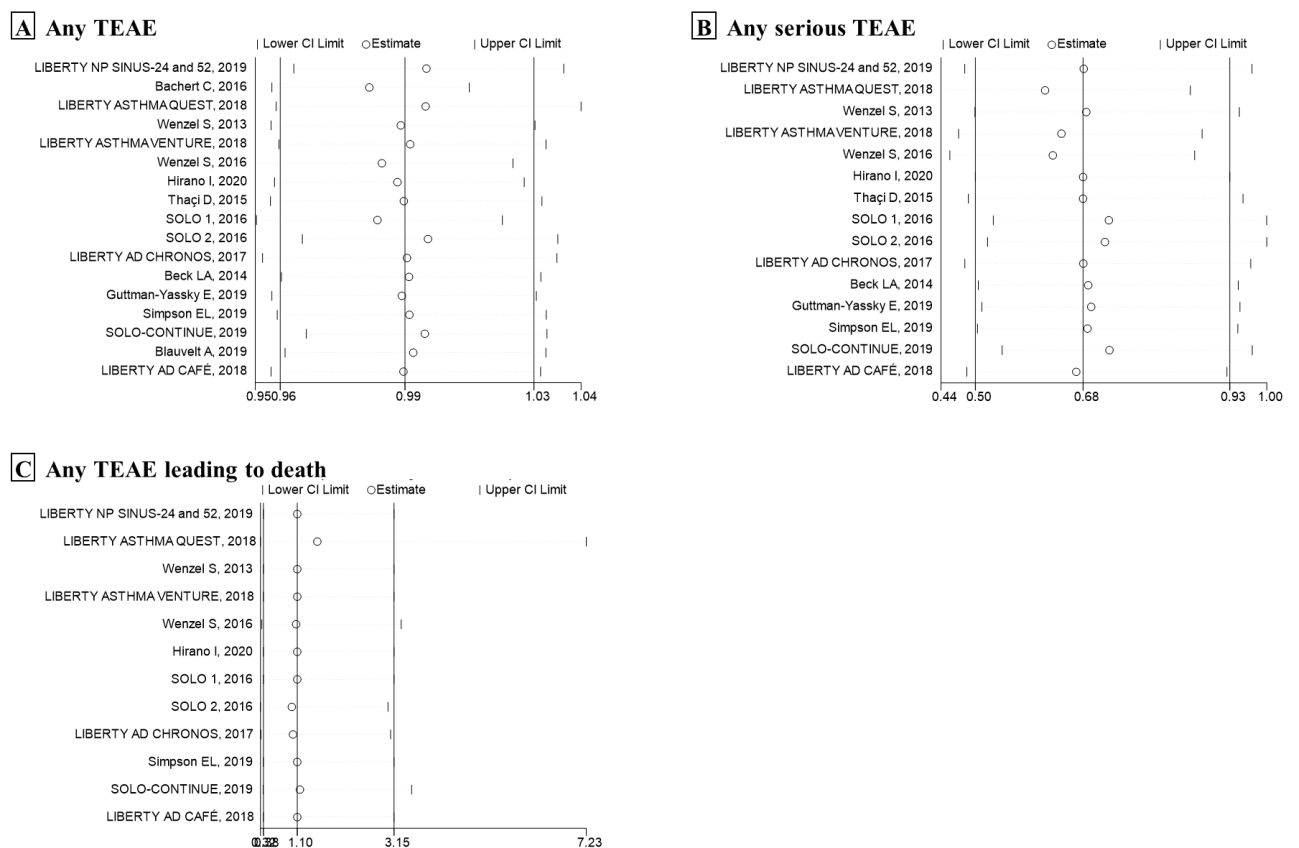


Figure S4. Sensitivity analysis of any treatment-emergent adverse event (TEAE; A), any serious TEAE (B), and any TEAE leading to death (C). After removing each RCT, the remaining RCTs were in agreement with the previous meta-analysis.

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